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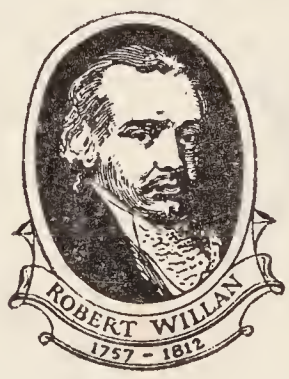

Presented by Dr. Anning

CD. 72632

THE

HISTOPATHOLOGY

OF THE

DISEASES OF THE SKIN

PRINTED BY TURNBULL & SPEARS

FOR

WILLIAM F. CLAY, 18 TEVIOT PLACE, EDINBURGH.

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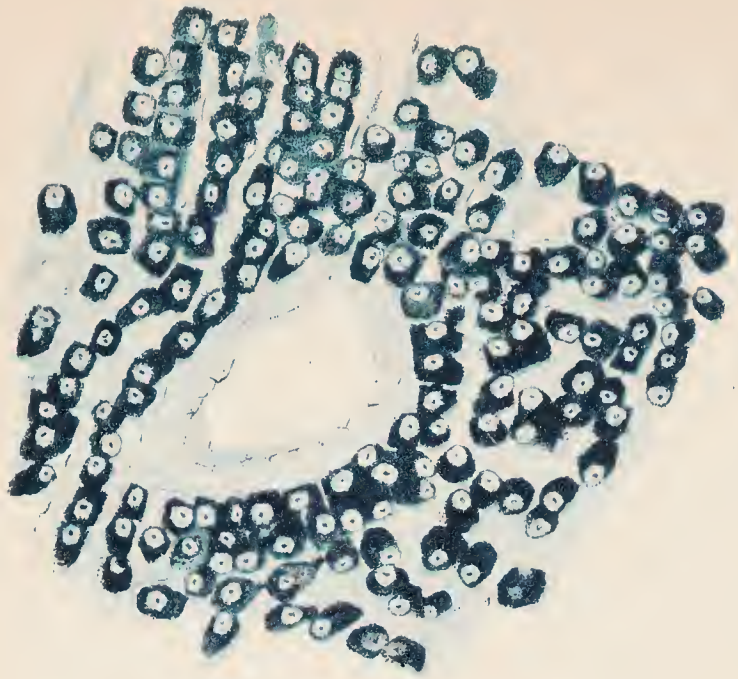
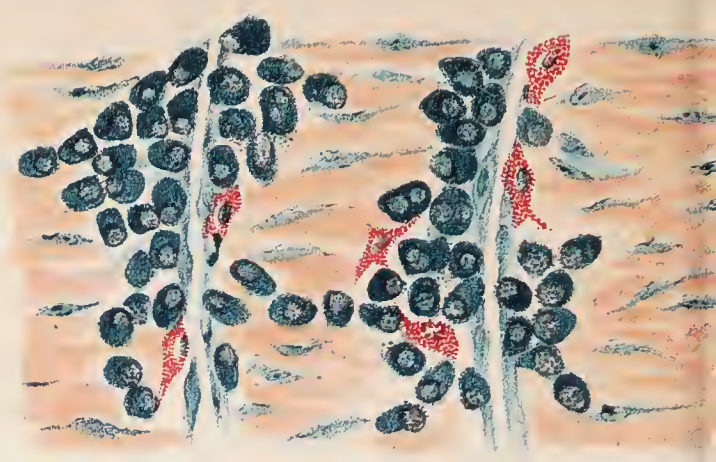
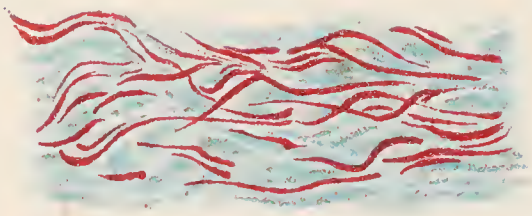


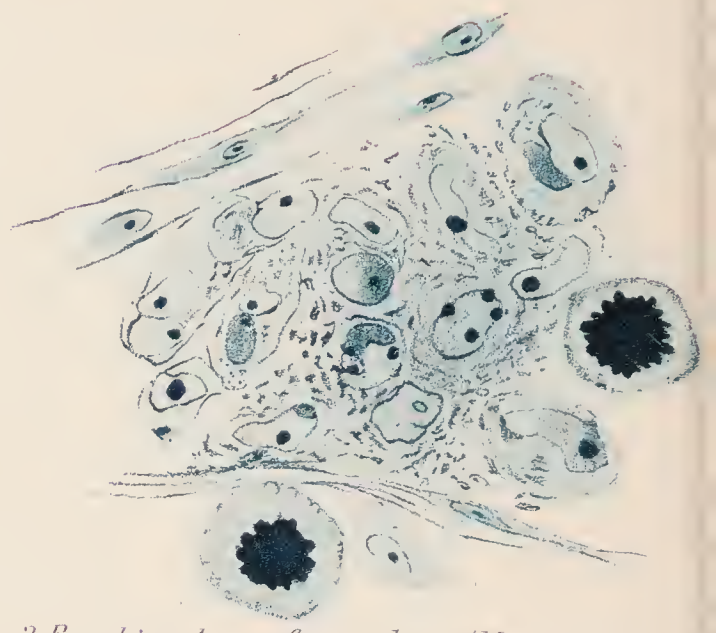
1. Plasma cells (Framboesia).



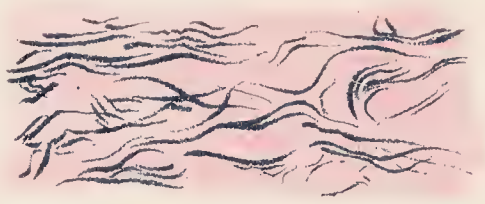
2. Plasma cells (Paget's disease).



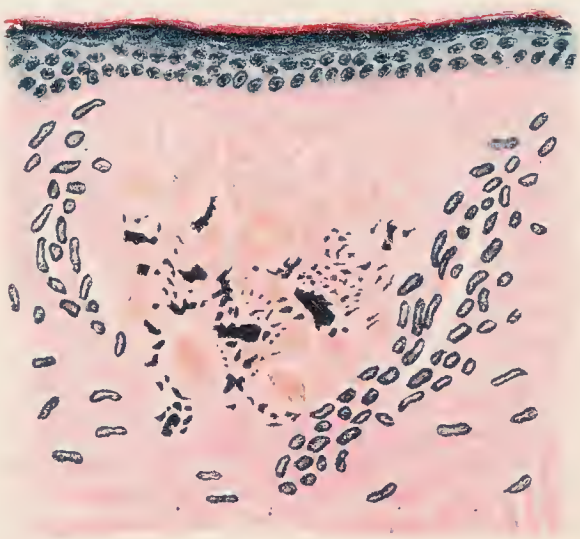
4. Elacin (Senile degeneration of the skin of the face).



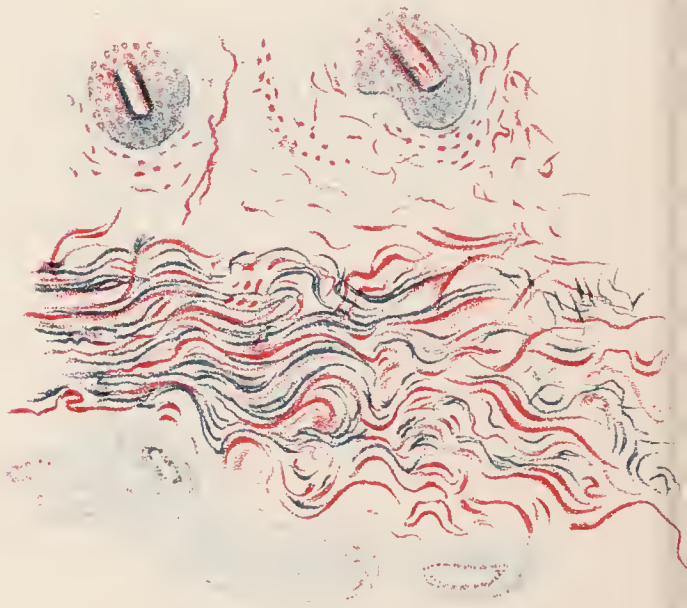
3. Breaking down of protoplasm (Myrosis fungoides).



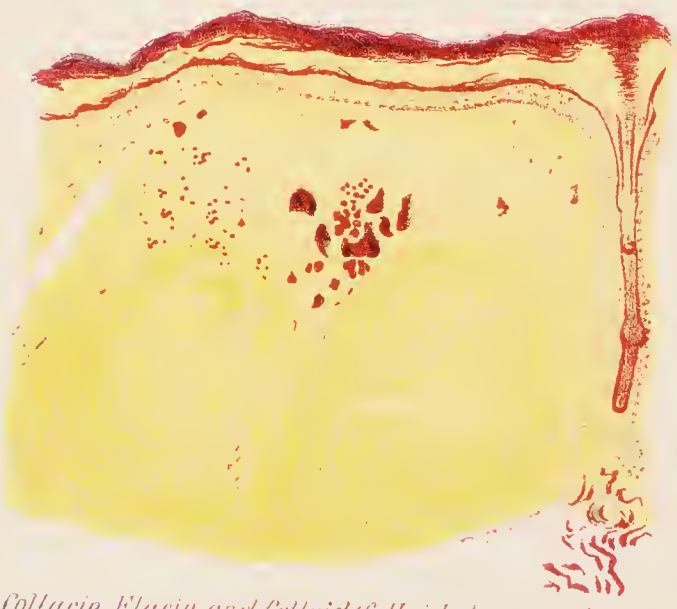
5. Elacin (Senile degeneration of the skin of the face).



6. Collacin (Senile degeneration of the skin of the face).



7. Elacin (Myxoedema).



8. Collacin, Elacin and Colloid (Colloid degeneration).

9. Collastin and Colloid (Colloid degeneration).

EXPLANATION OF PLATE.

1. PLASMA CELLS.

FRAMBŒSIA.

Polychromic methyl-blue, glycerine ether.—Specific protoplasm stain. Collagen and nuclein decolourised ; only protoplasm and nucleoli stained. The growth consists entirely of large round or cubical plasma cells (p. 505).

2. PLASMA CELLS.

PAGET'S DISEASE.

Polychromic methyl-blue, neutral orcein.—The collagen has taken the orcein stain, protoplasm and nuclei blue, the mast cell granulation red. The cellular infiltration of the carcinoma consists of plasma cells (p. 744).

3. BREAKING DOWN OF PROTOPLASM.

MYCOSIS FUNGOIDES.

Polychromic methyl-blue, glycerine ether.—Protoplasm stain. Nuclei, except the nucleolus and the mitotic figures, decolourised. Fragments of protoplasm fill the lymph spaces (p. 510).

4. ELACIN.

SENILE DEGENERATION OF THE SKIN OF THE FACE.

Water-blue, carbolic fuchsin.—Collagen fibres blue, basophilic elastic (elacin) red (p. 980).

5. ELACIN.

SENILE DEGENERATION OF THE SKIN OF THE FACE.

Methyl-blue, acid fuchsin and tannin.—Collagen fibres red ; basophilic elastic (elacin) blue (p. 980).

6. COLLACIN.

SENILE DEGENERATION OF THE SKIN OF THE FACE.

Methyl-blue, acid fuchsin and tannin.—Collacin is found in the upper part of the cutis, underneath the subepithelial elastic convolution and inside degenerated areas of collagen, in the form of granules, fragmented masses and angular portions, all coloured deep blue (p. 981).

7. ELACIN.

MYXŒDEMA.

Water-blue, carbolic-fuchsin.—The central portion of the cutis between the sections of two hair follicles and the vessels and nerves beneath shows, in addition to blue collagen fibres, numerous red elacin fibres, some of which permeate the looser upper portion (p. 994).

8. COLLACIN, ELACIN AND COLLOID.

COLLOID DEGENERATION.

Acid fuchsin, picric acid, water and alcohol.—The colloid degeneration affects the areas of skin between the hair follicles to the right and the epithelial ridge to the left. The part in the lower right hand corner is most affected. In the extreme right corner are some elacin fibres, and in the centre above some blocks and granules of collacin stained red (p. 991).

9. COLLASTIN AND COLLOID.

COLLOID DEGENERATION.

Acid orcein, hæmatoxylin.—A portion of the cutis between the lanugo follicles shows on the right the mature colloid substance in homogeneous blocks, on the left its development from a felt-work of collastin fibres, which clear up and become homogeneous from the centre towards the periphery (p. 990).

10. BALLOONING DEGENERATION OF EPITHELIUM.

VARICELLA.

Polychromic methyl-blue, neutral orcein.—Low power drawing of varicellous vesicle. Three septa surrounded by ballooned and giant epithelia divide up the cavity. The epithelia are also seen loose at the base (p. 637 *et seq.*).

EXPLANATION OF PLATE.

11. BALLOONING DEGENERATION OF THE EPITHELIA.

ZOSTER.

Gentian-violet, iodine anilin. — Portion of a Zoster vesicle. Ballooned epithelia of every form and size, some with numerous nuclei scattered loosely in the under part of the vesicle, while the upper part is filled partly with elongated fibrinoid epithelia and partly with fibrin (p. 151 *et seq.*).

12. BALLOONING DEGENERATION OF THE EPITHELIA.

VARICELLA.

Polychromic methyl-blue, neutral orcein.—Ballooned epithelia from the base of a vesicle, becoming loosened from the cells at the base of the vesicle (p. 637 *et seq.*).

13. RETICULATING DEGENERATION OF THE EPITHELIA.

VARIOLA.

Polychromic methyl-blue, neutral orcein.—Conversion of the epithelia into elementary vesicles, by colliquation of the endoplasm, the nucleus and the outer cell wall being preserved (p. 635 *et seq.*).

14. PLATE CELLS.

GRANULATION TISSUE.

Polychromic methyl-blue, alcohol plus Xylol.—Horizontal section of an old granulation. Between the collagenous plates there lie, also horizontally, large, multinuclear plate cells of trapezoid form, which are connected by processes of their spongioplasm (p. 830).

15. CHROMATOTEXIS.

GLANDERS.

Methyl-blue, acid fuchsin and tannin.—Liquefaction of the chromatin in an acute nodule. To the right is a necrotic vessel. The collagen and protoplasm have run together to a homogeneous necrotic mass, which is coloured pink by the acid fuchsin (p. 462 *et seq.*).

16. MAST CELLS WITH HALOES.

NEUROFIBROMA.

Polychromic methyl-blue, neutral orcein.—Neurofibromatous fibres have taken the orcein stain. The connective tissue cells and nuclei are blue, mast cells methyl-red. On the right is an ordinary mast cell, the other three have the halo (p. 847).

17. HYALIN DEGENERATION OF THE CONNECTIVE TISSUE CELLS.

ACTINOMYCOSIS.

Methyl-blue, acid fuchsin and tannin.—A few leucocytes are present. The hyalin degeneration of the connective tissue cells leads to the formation of perfectly homogeneous rosy cells, or to the occurrence of dark red homogeneous spheres along with the well-preserved nucleus and certain portions of well-preserved blue protoplasm. These cells ultimately break up into collections of hyalin spheres (p. 468).

18. XANTHOMA MASSES.

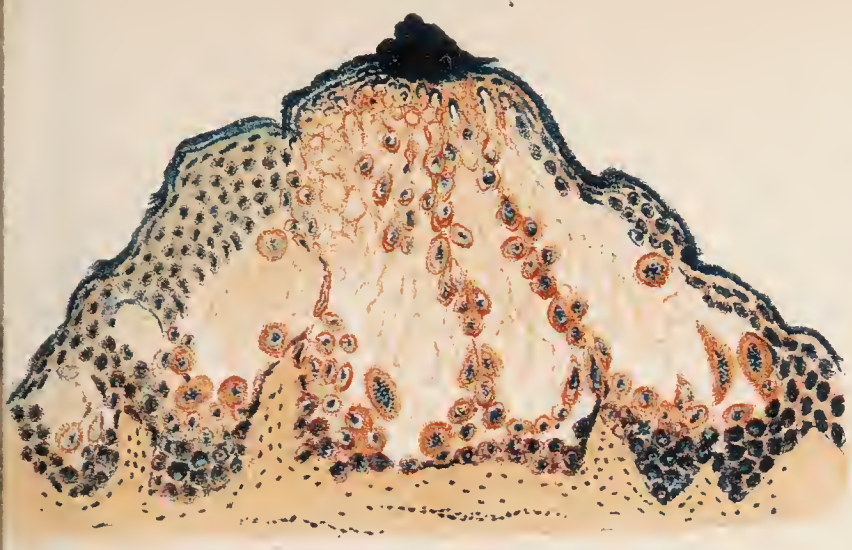
XANTHOMA OF THE EYELIDS.

Fixed in Flemming's solution. Water-blue, carbolic-fuchsin.—The yellowish, fish-roe-like Xanthoma masses fill the lymph spaces of the cutis, and often enclose one or more connective tissue nuclei. They correspond to "Xanthoma cells" (p. 948).

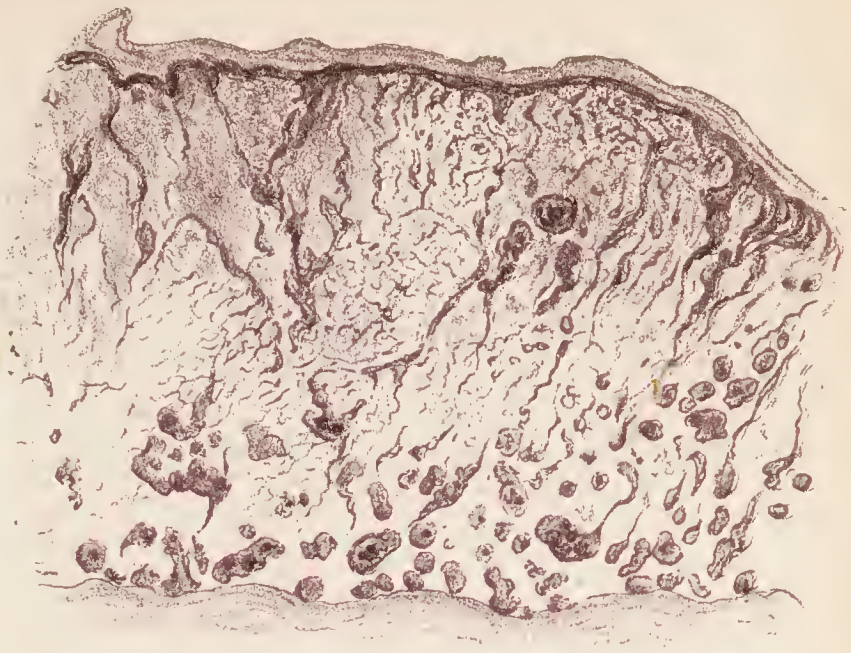
19. XANTHOMA MASSES WITH GIANT CELLS.

FIBRO-XANTHOMA GIGANTO-CELLULARE MULTIPLEX.

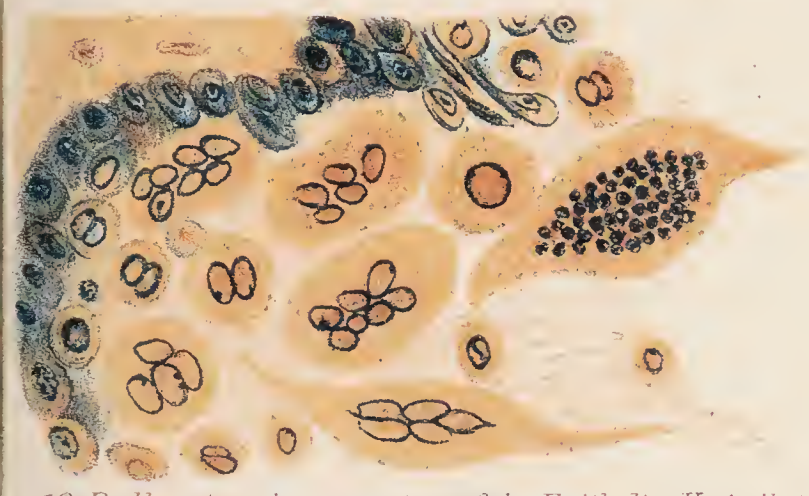
Fixed in osmic acid. Methyl-blue, tannin.—The giant cells with their rings, rarely collections of nuclei, are surrounded by the xanthoma masses, which fill all the spaces of the collagenous tissue (p. 954).



10. Ballooning degeneration of the Epithelia (Varicella).

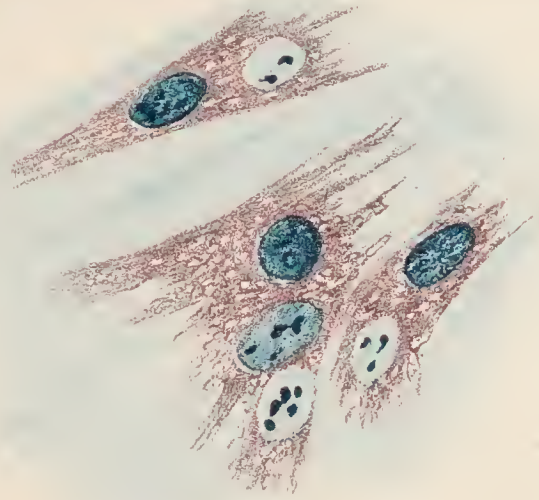


11. Ballooning degeneration of the Epithelia (Zoster).

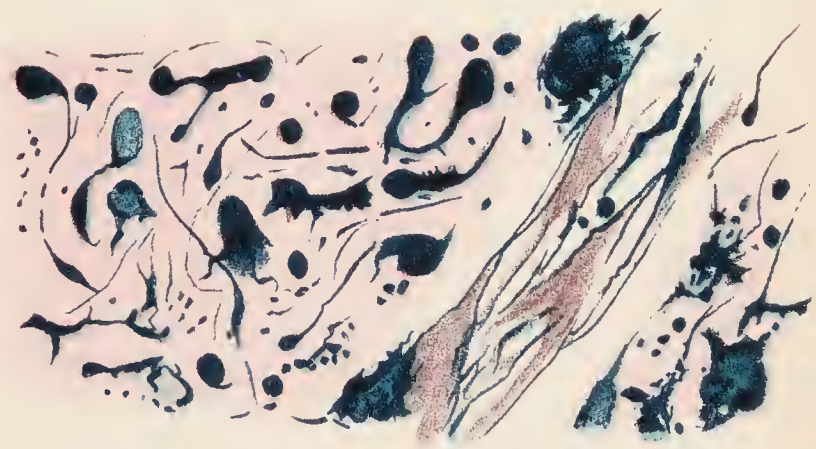


12. Ballooning degeneration of the Epithelia (Varicella).

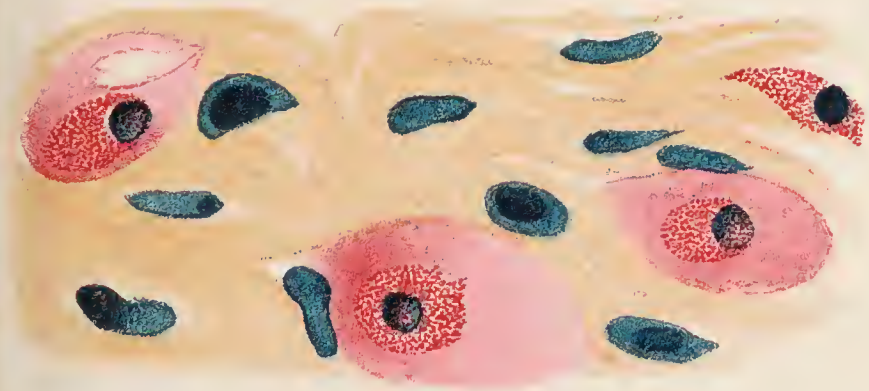
13. Reticulating degeneration of the Epithelia (Variola).



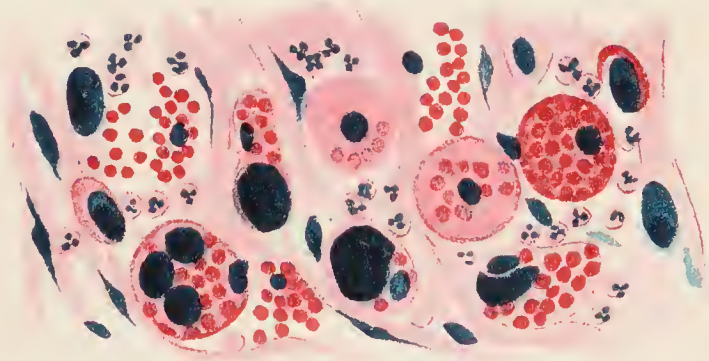
14. Plate cells (Granulation tissue).



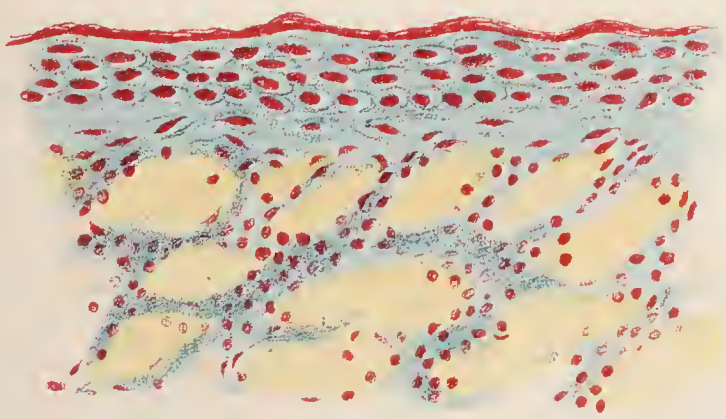
15. Chromatotexis (Glanders).



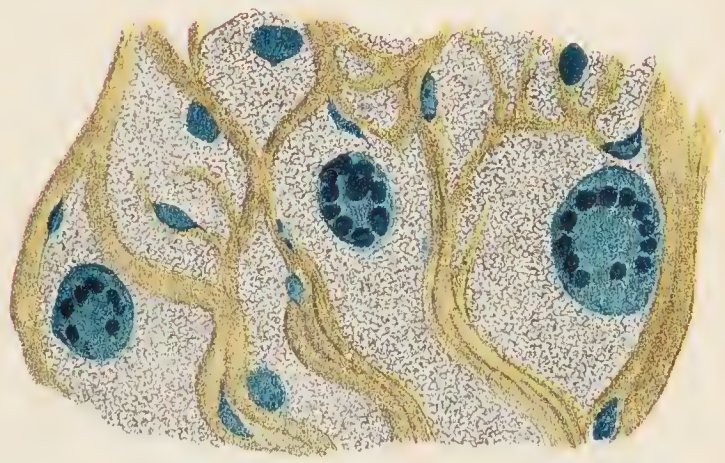
16. Mast cells surrounded by halos (Neurofibroma).



17. Hyalin degeneration of the connective tissue cells (Actinomycosis).



18. Xanthoma masses (Xanthoma of the eyelids).



19. Xanthoma masses with giant cells.

THE

HISTOPATHOLOGY

OF THE

DISEASES OF THE SKIN

BY

DR P. G. UNNA

TRANSLATED FROM THE GERMAN WITH THE ASSISTANCE OF THE AUTHOR

BY

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ASSISTANT PHYSICIAN IN DERMATOLOGY TO THE ROYAL INFIRMARY, EDINBURGH

WITH DOUBLE COLOURED PLATE CONTAINING NINETEEN ILLUSTRATIONS
AND FORTY-TWO ADDITIONAL ILLUSTRATIONS
IN THE TEXT

EDINBURGH

WILLIAM F. CLAY, 18 TEVIOT PLACE

NEW YORK: MACMILLAN & CO.

1896

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AUTHOR'S PREFACE.

The first text-book on the histopathology of the skin appeared in 1840, when Gustav Simon published the results of his years of study, to which he had been stimulated by the publication of several works on the normal anatomy; in particular, that of the elder Krause. His work was, and still is, one of great value.

This was followed by an active period, during which a great number of observations saw the light, though it was not a time favourable to that arrangement necessary in a text-book. It is especially to be regretted that Virchow's great work, which did so much for general pathology, was wanting in its reference to cutaneous pathology. And Hebra's work also practically ignores the subject, though Hebra sought to use pathological anatomy—at least in the systematisation of disease.

The recent Atlas of Leloir and Vidal has the same object as the present work, but since it proceeds on different lines, the two rather amplify than oppose each other. In the Atlas, the plates are the most important element, while a thorough clinical description of the cases makes the work a sort of text-book of skin diseases. The object of this work—as a part of Orth's system—is only to give a thorough description of the pathological anatomy of all the dermatoses, so far as our present knowledge extends.

But when, five years ago, the subject was put before me, it seemed to me that there was another and a wider sphere opened, and I soon saw that the work was bound to exceed in extent the other volumes of the system. For, with a few unimportant exceptions, we have, in connection with the skin, two very great advantages. Firstly, we can always get fresh, *living* material for investigation; and secondly, we are able to observe the part, and to note its relation to the disease as a whole, before excision. This exceptionally favourable position brings with it a two-fold responsibility. The first is clinical. For since it is possible to compare the clinical appearances with the histological details, it is our duty closely to analyse them, to investigate every apparent disharmony, and not to rest till we have brought the macro- and microscopical appearances into agreement one with the other.

It is at once apparent that this thorough study of cutaneous pathology must have a great bearing on general pathology. Inflammation and the formation of tumours have a very close relation to the skin, for there they can be observed with the naked eye. A whole series of processes are visible only on the skin; perhaps they occur in the internal organs, but they are no longer visible on the corpse. How can we become familiar with them, if not by comparison with similar processes on the skin? The facts noted in the chapters on Anomalies of Circulation and Neurotic Inflammations have perhaps their counterpart in some in neuro-pathology; the catarrhs of the mucous membranes, so obscure in their nature, may perhaps be illuminated by a knowledge of the catarrhs of the skin, etc., etc. A dermatologist cannot venture to explain everything in these—to him—strange territories, but it is all the more his duty to establish, with all possible precaution and patience, those conditions of the skin which admit of such comparison, so that the investigators of other organs may make it for themselves. So in every obscure affection of the internal organs we shall find some analogous, better known affection of the skin, which will serve to make this clear.

A summary of the literature soon made it evident to me that there was no real histopathology of the skin, that there was but little harmony between clinical and histological detail, and that to the clinician, microscopical observation had been more troublesome than useful. It is indeed not to be wondered at, that very eminent dermatologists, even those whose clinical experience is of the utmost value, turn with impatience from present day histopathology, where all the inflammations of the skin seem to be microscopically alike. The fact that, in most dermatological text-books, the microscopical anatomy is merely a sort of ornamental addition, is but too well justified; for when two skin diseases, clinically distinct, give, microscopically, the same appearances, or where the microscope shows differences where clinically none exist, it is clear that something wants elucidation. Certain facts, fortunately rapidly increasing, we do know, but unfortunately they are mostly in connection with the rare diseases—Pityriasis rubra pilaris, Epithelioma contagiosum, Darier's disease, Leprosy, Myoma, etc. So far they achieve the true aim of all pathology, the enlightenment of clinical work. But the common everyday diseases—Eczema, Acne, Vesicular diseases, Trichophytosis, Favus, Syphilis, have only a very meagre literature.

The tumours of the skin are in much the same position, except that here we sometimes have the help of the pathologist. I need only instance Virchow's masterly description of Angioma and of Onychogryphosis, and that of Neurofibroma by v. Recklinghausen.

But the majority of publications are too often vague and little characteristic, and many of them, from the insufficient information they give about the seat or stage of the disease, are not only useless, but have actually been applied by other authors to other conditions. This has led to the accumulation of a great number of contradictory statements, which, by their stereotyped reproduction in all literature (especially dissertations), appear under the cloak of science. This is the unfortunate position of the great majority of our most important skin diseases.

There were thus two methods open to me. I might either content myself with simply repeating the different statements, critically sifting them, and endeavouring to disentangle the great literary confusion, rejecting what was useless, and concluding most chapters with an ignoramus—a somewhat fruitless though not very difficult proceeding. Or, I might attempt, as Gustav Simon did, to work once more through the whole of cutaneous pathology—a labour certainly beyond the power of one individual, and the short period of five years. I have preferred to do this incompletely, and to leave its amplification to the future, rather than to give a mere dreary retrospect.

The acquisition of material was a great difficulty. I had indeed my private clinic and two polyclinics, which were fully made use of. But without the kind assistance of Drs v. Esmarch, Gutsch, Lauenstein, and Sick, who supplied me with much material from operations; of the surgeons of the general Hospital in Hamburg; and of the prosectors, Dr Eugen Fraenkel and Dr Simmonds, whom I have to thank for abundance of material from the corpse, I would certainly not have been able to complete this work. I take this opportunity of expressing my warmest thanks to them, as well as to all those dermatologists to whom I owe material and preparations, and who are named throughout the book.

A second difficulty, not so easily overcome, was that of methods. It is owing to the deficiency in these, that so many skin diseases appear alike microscopically, and that a microscopic diagnosis, without some knowledge of the clinical aspect, is often impossible. The older methods are nearly all nuclear stains, and it cannot be denied that many of them, especially the mitotic stains of Flemming, have helped us in the estimation of many pathological processes, especially of the reproduction of the different constituents of the tissues. On the other hand, everyone will admit that most important changes occur in the protoplasm of the cells. There we find the main differences in the diseases; there alone can we in many cases study the history of skin disease. The nuclei, so long as they are not pathologically altered, maintain a perennial youth. They are the productive organs of the

tissues, and are not suitable indicants of the finer changes which occur. It is to be regretted that so many workers on cutaneous pathology are satisfied with the simple recognition of "young" or "embryonic" connective tissue, for these expressions simply mean collections of nuclei; and it is easy to see how anyone using these terms would find it difficult to distinguish between the statements of Virchow and Cohnheim, as to the origin of these embryonic cells. Little advance is made by using the word "round" instead of "embryonic" cells, for the meaning is the same.

This confusion must be cleared up, and this can only be done by the use of specific staining methods for the protoplasm.* After these had been tested in the relatively easy discovery of plasma cells, they were gradually perfected, until the protoplasmic body of the connective tissue cells of the normal cutis was disclosed.

But in addition to living protoplasm, the skin contains masses of by no means inactive interstitial tissue. This was evident with these nuclear stains; but it was necessary, here also, to discover specific stains for each individual intercellular substance. After the staining of the elastic tissue, came the specific stain of collagen, then that of the degeneration products and intercellular substance, of hyaline, mucinous and fibrinoid masses, and finally, of elacin, collacin, and collastin.

Further, the dense staining of the horny substance requires special methods, in order to determine the presence of bacteria in it.

With all these adjuvants, it is no longer remarkable that most skin diseases not only do not look alike, but even show such an abundance of histological peculiarities, that their explanation must be for the present postponed. But we may hope, that with continuous improvements in methods, it will not be long before the histological diagnosis of the different dermatoses is on a level with the clinical. At all events, these new methods, incomplete as they are, have enabled me more thoroughly to understand many old views, and to bring many apparently contradictory statements into accord.

On account of the ever-increasing improvement in methods, certain chapters are not so complete as others, although an attempt has been made to remedy this by a revision of the older chapters. But a complete revision was not possible.

I have, for a special reason, always placed a short clinical diagnosis at the head of each chapter. This was a most necessary caution, for many unnecessary contradictions in literature have arisen from slip-shod diagnosis. Investigators had before them different material,

* All these methods have been published by me in the Monatsheften für praktische Dermatologie.

while they professed to be investigating the same. It may be that different stages of the same affection were examined, or affections altogether different, and only erroneously named alike (true Ichthyosis and Keratoma, Fibroma and Neurofibroma, Acne and any other kind of folliculitis, etc.). This is a source of constant error, which should in future be entirely avoided. In this work, my own histological statements always relate only to the affection as clinically described.

I have everywhere directed my attention to the gaps in our knowledge, and have tried to indicate what is necessary for their supply. The important elementary changes of the protoplasm and intercellular substance are shown on the coloured plate.

I have simplified the nomenclature as much as possible. Following the English, I have named the excretory duct of the sweat gland the "duct"; there are no other ducts in the skin. The sweat glands are frequently called "coils"; the hair follicle along the sebaceous gland, shortly, "follicle." The internal root sheath I call, for the same reason, the "root sheath," for the so-called external root sheath does not belong to the hair but to the follicle, the prickle layer of which it represents. The unnecessary long expressions "granular cell layer" and "prickle cell layer" are always replaced by "granular layer" and prickle layer," for there is nothing but cells in the epithelium. The old name "rete Malpighi" for the prickle layer is abandoned, for it is not, as Malpighi thought, a net; and the persistent use of this name only gives support to a long-standing error. If the great Malpighi, to whom we owe so much, still lived, he would be the first to admit that it was incorrect to regard the epidermis as a soft net with a horny covering (instead of a plate having ridges beneath, and being cornified above). It sounds trite, but it is evidently still necessary to draw attention to the fact, that by the epidermis we mean the whole epidermis, and not, as implied in numerous works, even dermatological ones, simply the horny layer. The more exact descriptions of pathological changes in the coils and ducts are derived from the Greek words "spira" (coil), and "syrinx" (narrow duct), *e.g.*, Spiradenitis, Syringadenoma, perispiral. The new diseases described in this book make it necessary to form new adjectives, and these are always so chosen that the last syllable, "genes," indicates produced by, while the last syllable, "phoros," means producing, inducing. Thus, Impetigo staphylogenes, Impetigo streptogenes mean impetigo induced by staphylococci or streptococci; pyophoric organisms are "pus-producing organisms." The attraction of chemotactically drawn substances is indicated shortly as serotaxis (attraction of serum), leucotaxis (attraction of leucocytes), fibrinotaxis, and sebotaxis.

In conclusion, I have to thank my former assistant, Dr Taenzer

(Bremen) for the preparation of the index, and for his valuable assistance in preparing the reviews of literature; as well as my laboratory assistant, Mr Max Colhoun, for his unwearied exertion in working through the histological material.

I publish the book in the hope that it will make new friends among the pathologists for dermatology, and among dermatologists for microscopic anatomy.

UNNA.

HAMBURG, *June* 1894.

TRANSLATOR'S PREFACE.

Dr Unna's name is too well known to render it necessary to preface this translation of his great work by any apology. Of its importance it is hardly necessary to speak. Dermatology has rather lagged behind other departments of medicine, largely on account of the want of comprehension of the pathological conditions with which it deals; and while it would be too much to claim that Dr Unna has made all clear, he has undoubtedly laid the foundation and contributed much towards a better understanding of the Diseases of the Skin. The feeling of regret that the book does not deal directly with treatment, will vanish when it is carefully read. It contains the best of all indications for treatment, in pointing out what is at fault, and in many cases indicating the lines for its correction.

To Dr Unna I desire to tender my best thanks for his very valuable assistance in producing this volume. I pointed out to him that, to the English reader, illustrations were a *sine qua non*, and he at once put at my disposal his whole cabinet of drawings, and where I considered additional ones desirable, he had them prepared, under his direct supervision, by Herr Gummelt, who is well known to pathologists as the artist of "Kast & Rumpf's Atlas of Pathology." The drawing of Lupus which was sent me was too large, and the one used is made from one of my own preparations. The publisher has been at great pains to have the drawings carefully reproduced.

Dr Unna has also taken advantage of this edition to make certain alterations and emendations of the original; and some slips and errors, which had crept into the German text, have been corrected.

Many reviewers were good enough, in noting my translation of "Hansen on Leprosy," to congratulate me on the absence of foreign idiom. That in this case I have been equally successful, I cannot hope. The novel character of many of the subjects discussed, and the practical impossibility of translating some of the words into ordinary English, have made the translation a much heavier task than that of an ordinary text-book. Thus I am aware that "lumpy fragmentation" is rather quaint English, but I could not design any better translation for "Schollige Zerklüftung." Where such words first occur I have, as

a rule, also given the original German. Had I previously noted a paper by Dr Brooke, I would have used his translation, "flask bacillus," instead of "bottle bacillus." In this difficulty, Dr Unna's excellent knowledge of English has been of great value to me, and many of the words used were selected after discussion with him.

I am very much indebted to several friends—to Dr Brooke for permission to use his drawing of "Acanthoma adenoides cysticum," as well as for much friendly counsel; to Mr Dale James, Surgeon to the Skin Department of the Sheffield General Hospital; to my colleague, Dr Lovell Gulland; and to my former assistants, Drs. Wearne Clarke of Chesterfield, Crawford of Worksop, and Crichton of Dunbar, who were good enough to divide my typoscript among them, and to compare it with the original. To them much of the accuracy and clearness of the translation is due.

With Dr Unna, I would hope that the present volume may do much to stimulate the pathological investigation of skin diseases, and to open the eyes of pathologists to the vast and fruitful field which the skin presents for the investigation of the problems of general pathology.

NORMAN WALKER.

EDINBURGH, *January* 1896.

AUTHOR'S PREFACE TO ENGLISH EDITION.

(*Translation.*)

The Editor and Publisher of this English translation of my "Histopathology of the Skin" (published last year) wish to have a few introductory words from my pen. These can only be words of hearty acknowledgment. I know very well that the mere reading of my book presents difficulties, and that, on account of the numerous new methods on which it is based, it requires careful study. But the attempt to make the book live again in another language is a much more difficult task, and this is especially the case in English, where the brevity of expression alone must limit the long rhythm of the German construction. But so far as I understand English, the translation has been most successful, and indeed in many places its conciseness has a certain advantage over the original. Dr Norman Walker was evidently predestined for the work, for several visits to my Klinik had enabled him to become thoroughly acquainted with my pathological views; and his —may I say—Scottish energy has led him during this last year no fewer than three times to Hamburg, in order to discuss with me personally certain minor, but important, alterations in them. This has undoubtedly added to the value of the work. The numerous drawings made from preparations from my laboratory will also be looked on by the English reader as a great improvement on the original.

I hope that this translation will do much to forward, on the other side of the channel and the Atlantic, the study of the subject of Cutaneous Pathology, which at present appears to be in a condition of vigorous growth.

UNNA.

Hamburg, *Dec.* 1895.

INDEX OF AUTHORS REFERRED TO.

THE names printed in capitals usually indicate those works in which the reader will find the literature of the subject most complete. Sometimes the capitals signify that the work is of exceptional value.

In view of the constantly recurring titles of text-books, monographs, and journals, the following abbreviations are used :—

LEBERT : *Lebert*, Physiologie pathologique. Paris, 1845.

FÖRSTER : *Förster*, Handbuch der allgemeinen pathologischen Anatomie. Leipzig, 1865.

VIRCHOW : *Virchow*, Die krankhaften Geschwülste. Berlin, 1863.

RINDFLEISCH : *Rindfleisch*, Lehrbuch der pathologischen Gewebelehre. 2. Auflage. Leipzig, 1871.

LÜCKE : *Lücke*, Die Lehre von den Geschwülsten. 1869, in Pitha-Billroth's Handbuch der Chirurgie.

UHLE und WAGNER : *Uhle* und *Wagner*, Handbuch der allgemeinen Pathologie. Leipzig, 1874.

COHNHEIM : *Cohnheim*, Vorlesungen über allgemeine Pathologie. Berlin, 1882.

v. RECKLINGHAUSEN : *v. Recklinghausen*, Handbuch der allgemeinen Pathologie. Stuttgart, 1889.

ZIEGLER : *Ziegler*, Lehrbuch der allgemeinen und speciellen pathologischen Anatomie. 5. Auflage. Jena, 1887.

KLEBS : *Klebs*, Allgemeine Pathologie. Jena, 1889.

BAUMGARTEN : *Baumgarten*, Lehrbuch der pathologischen Mykologie. Braunschweig, 1890.

WINIWARTER : *Winiwarter*, Die chirurgischen Krankheiten der Haut und des Unterhautzellgewebes. Stuttgart, 1892.

WILLAN : *Willan* und *Bateman*, Praktische Darstellung der Hautkrankheiten. Deutsch v. Blasius. Leipzig, 1835.

RAYER : *Rayer's* theoret.-prakt. Darstellung der Hautkrankheiten. Deutsch von Stannius. Berlin, 1837.

GIBERT : *Gibert*, Traité pratique des maladies spéciales de la peau. Paris, 1840.

G. SIMON : *G. Simon*, Die Hautkrankheiten, durch anatomische Untersuchungen erläutert. Berlin, 1848.

WILSON : *Erasmus Wilson*, Die Krankheiten der Haut. Deutsch von Schröder. Leipzig, 1850.

F. HEBRA : *Hebra* u. *Kaposi*, Lehrbuch der Hautkrankheiten. Stuttgart, 1876.

KAPOSI : *Kaposi*, Pathologie und Therapie der Hautkrankheiten. 3. Aufl. Wien und Leipzig, 1887.

NEUMANN : *Neumann*, Lehrbuch der Hautkrankheiten. 4. Aufl. Wien, 1874.

AUSPITZ : *Auspitz*, System der Hautkrankheiten. Wien, 1881.

Schwimmer: *Schwimmer*, Die neuropathischen Dermatosen. Wien und Leipzig, 1883.
Duhring: *Louis A. Duhring*, Traité pratique des maladies de la peau, traduit et annoté par Barthélémy et Colson. Paris, 1887.
M'Call Anderson: *M'Call Anderson*, A treatise upon diseases of the skin. London, 1887.
Piffard: *Piffard*, An elementary treatise upon diseases of the skin. New York, 1876.
Morrow: *Morrow*, Drug eruptions. New York, 1887.
White: *White*, Dermatitis venenata. Boston, 1887.
Crocker: *Crocker*, Diseases of the skin. London, 1888.
Jamieson: *Jamieson*, Diseases of the skin. Edinburgh, 1888.
v. Ziemssen: *v. Ziemssen*, Handbuch der Hautkrankheiten. 14. Bd. des Handbuches der speciellen Pathologie und Therapie. Leipzig, 1883-1884.
Behrend: *G. Behrend*, Die Hautkrankheiten. Braunschweig, 1879.
H. Hebra: *H. Hebra*, Die krankhaften Veränderungen der Haut. Braunschweig, 1884.
Lesser: *Lesser*, Lehrbuch der Hautkrankheiten. 3. Aufl. 1887.
Besnier-Doyon: Pathologie et traitement des maladies de la peau par Kaposi Notes et additions par *Besnier* et *Doyon*. Paris, 1881.

V. A.: *Virchow's* Archiv.
A. A.: *Auspitz's* Archiv: Archiv für Dermatologie und Syphilis. 1869-1873. Vierteljahrsschrift für Dermatologie und Syphilis. 1874-1888. Archiv für Dermatologie und Syphilis. 1889-1894.
Mon.: Monatshefte f. praktische Dermatologie. Hamburg, 1882-1894.
Annales: Annales de Dermatologie und Syphilographie. Paris, 1869-1894.
Giorn.: Giornale italiano delle mallatie ven. e della pelle. Milano.
Journ. of cut.: Journal of cutaneous and genito-urinary diseases. New York.
B. J. D.: British Journal of Dermatology. London.
B. M. J.: British Medical Journal.

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THE HISTOPATHOLOGY

OF THE

DISEASES OF THE SKIN.

Section I.

ANOMALIES OF CIRCULATION.

Our first difficulty is in dealing with the remarkable confusion between clinical and anatomical observations. We have presented to us an apparently inexhaustible and daily increasing wealth of clinical forms, the anatomical explanations of which are not only few in number, but somewhat tedious and uninteresting in their monotony. The cause of this is partly due to the fact that the anomalies of circulation are chiefly functional in their nature. A post-mortem examination can give us just as little information about purely functional disturbances of circulation as it can about anomalies of sensation, which disappear the moment the nerve is cut. All we can discover from a post-mortem, are either preliminary changes in the tissues (*e.g.* obliteration of the vessels) accompanying changes (*e.g.* deposit of pigment) or some more durable condition brought about by the anomaly of circulation (*e.g.* hæmorrhage). From these observations we draw our conclusions as to what has been the clinical condition of the vascular and lymphatic systems. But part of our ignorance is due to the, as yet, imperfect condition of our methods, and we must persevere in our efforts to improve these.

A great step has been gained in that, wherever possible, we use for investigation pieces of skin removed from the living, rather than the dead, thus substituting a zoopsy for a necropsy. By methodical improvements in the manner of removing the skin, by rapidly fixing it in its existent condition and retaining it so until under the microscope, we shall undoubtedly succeed in preserving even the finer changes in the circulation for anatomical demonstration. And as with the excep-

tion of the eye, the skin is the only organ in which we can compare the histological appearances with the clinical, it is our duty in the interests of the internal organs, clinically hidden from us, so far as possible, to complete the anatomical investigation of the anomalies of circulation in the skin. There is moreover in the skin a whole class of disturbances of circulation, the angio-neuroses, the examination of which is open to us and whose existence in other organs we can only —as in hysterical affection of the nervous system—suspect.

It seems to me then advisable in this chapter on anomalies of circulation even more than in the other, to lay stress not only on the histological aspects but on the gross anatomical, the topographical, and the clinical, on this last only so far as it may help to clear up our general pathological knowledge of these anomalies. I hope thus not merely to provide a temporary stop-gap for this yawning chasm in our anatomical knowledge, but also by a general marshalling of the manifold facts, which complicate the investigation, to attract the interest of the pathologist more than formerly to this difficult subject. As indicated in the Preface, I follow a definite arrangement and introduce the special chapter, angio-neurosis, between the chapters hyperæmia and œdema.

A. ANÆMIA.

By anæmia of the skin we understand clinically two totally distinct kinds of pallor of skin, one a true deficiency of blood in the capillaries of the skin, the other a deficiency in its colouring material. This latter, being only a consequence of the general change in the systemic blood, its anatomical investigation must be looked for along with that of the disease of which it is a part (Chlorosis, Leukæmia, Hydræmia, destruction of the blood corpuscles by poison) under the pathology of the blood. We will only occupy ourselves with the *quantitative* diminution of the blood in the cutaneous vascular system.

This is either a manifestation of the diminution of the systemic blood or a condition restricted to the skin. We find the first in acute form in hæmorrhage after wounds, in severe intestinal or pulmonary hæmorrhage, and in chronic form in loss of blood caused by intestinal parasites and in the advanced stages of cachectic diseases (tuberculosis, cancer), accompanied in these last conditions with definite qualitative changes as well. In these symptomatic anæmias the skin plays in general the *rôle* of a regulator, for by the contraction of its vessels the remaining blood is transferred in increased quantity to the vital organs. For this *rôle* the skin is more suited than any other organ, for not only are the arteries and veins, during their subcutaneous course, supported by a particularly strong muscular coat, but the colla-

genous net-work in which they are embedded is maintained in a state of tension by the smooth muscles of the skin, and the remarkably rich net-work of twisted elastic fibres inserted into these muscles like tendons. Every piece of skin excised during life gives by its diminution, the place from whence it comes by its enlargement, proof of this internal cutaneous pressure. In consequence of these anatomical characters the skin forms the natural regulator in the case of loss of blood. We must not look upon the normal circulation in the skin as upon the comparatively simple circulation through the bones and lungs with their vessels and tissues poor in muscle; but rather look on it as, with the assistance of restraining ganglia, controlling the high pressure in the skin and the blood leaves the skin at once, when the total amount does not force some into the skin.

It is evident that for the production of an **isolated anæmia** of the *whole skin* with retention of the normal quantity of blood, proportionately powerful influences must be at work; and so we find pallor of the skin as a symptom of marked psychical disturbances, anxiety or fear, of severe injuries of sensitive nerves, in particular in the abdomen, and finally of a direct severe influence on the vasomotor centres as in rigors and in certain poisons (strychnin, ergot). In other cases the contracting influence of certain nervous causes is combined, in some unknown way, with the depletory action of the blood collecting in distant organs, as in fainting, intestinal nausea, in chronic alcoholism, and in excessive muscular or cerebral activity. Finally the skin undertakes a truly regulating function in cases of syncope, as is well seen in the ashy pallor accompanying angina. It is to this self-protecting power of the organism that we owe the fact, that on the post-mortem table the variegated aspect of most dermatoses appear only as monotoned colourless patches, only varied by the secondary products of the diseases, a fact all the more to be regretted, for to it is owing the little interest shown by the pathologist in these finer changes, which are only visible to the naked eye in the living skin. This usual absence of blood from the dead skin is, on the disappearance of the *rigor mortis*, replaced, in the dependent parts, by post-mortem lividity. It is only in very advanced degrees of stagnation in the peripheral circulation (death from heart disease) that there is no agonal vascular spasm of the skin.

More important in their etiological and clinical relations than the general anæmias of the skin, are the **circumscribed**. We can here always more definitely estimate the share which an almost concurrent primary diminution of the amount of blood plays in the primary diminution of the vessels. When for the purpose of a bloodless operation, or for anæsthesia, we elevate an extremity for any length of

time, the resultant anæmia is due to the locally diminished blood pressure, from the removal of a large quantity of blood. If on the other hand we constrict the limb in a dependent position, from below upwards, by means of an elastic bandage, the blood disappears secondarily, yielding to the primary compression of the vascular system. There follows in both cases on the restoration of the normal circulation, the familiar hyperæmia of the affected vessels, more marked in the latter case. Prolonged local anæmias of the skin from pressure on the circulation are very familiar. The pressure may be from without, as that of clothes, bandages or instruments, or it may be in or under the skin, as an abscess, an injection or a spastic œdema (Urticaria, Quincke's Œdema). The ligature of an artery will not cause a local anæmia of the skin so certainly as pressure, on account of the very profuse anastomosis of the capillaries of the skin. In ligature of the main artery of an extremity there is, before the development of the collateral circulation, a temporary anæmia.

Related to the pressure anæmias is a group of spastic anæmias of the skin, in which the cause of the partial absence of the blood is to be sought solely in the high degree of contraction of the vessel walls. There is also a pressure anæmia which is not mechanical in its production, like those already mentioned, but of a spastic nature. To a slight pressure, for example, the scratch of a pencil, the normal skin rapidly responds with a hyperæmic streak, which lasts from a half to one minute and is then followed by a similarly shaped anæmia, lasting from five to ten minutes. This depends on the direct irritation of the vessels, and is independent of the intervention of the central ganglia. Within physiological bounds, this process explains the pale colour of the skin in the inhabitants of southern climes, in bakers and machinists and in workers with fire in general. As the cold of the air excites, on the cheeks of the inhabitants of northern regions, a fresh red colour by persistent (compensatory) paresis of the vessels, so the constant existence in the warm air of southern regions causes a habitual (regulating) pallor of the cheeks. Under pathological conditions, this compensatory anæmia plays a *rôle* in connection with injured limbs where there is a tendency to stagnation and hypostatic congestion. It is the analogue to œdema from increased venous tone on such limbs. Much more important however, is Raynaud's disease, an idiopathic disease of a spastic nature which affects the ends of the fingers and toes, and belongs to the class of angio-neuroses. The milder forms of this disease are described as "dead fingers" or "local syncope," the more severe as "local asphyxia," but intermediate forms connect these two extremes and a sharp line of division cannot be drawn. This disease, limited to the vessels of the skin and sometimes going on to death of

the part, has for its immediate cause external cold, but we must nevertheless consider as lying at the bottom of it some special vulnerability of the vaso-motor system, as in all angio-neuroses. It affects the extremities only, because here alone can the external exciting cause operate at the same time on all the blood-vessels of a part, and thus the compensating anastomosis, which would occur elsewhere, is impossible. In this the affection resembles the stagnation which is produced on perfectly normal skin by severe cold, and which precedes frost-bite. It differs from this however in that in Raynaud the anæmia is complete and has a definite, sharply-defined margin; it comes and goes without any pricking pains or troublesome itching, and undergoes spontaneous periodic exacerbations in which external warmth produces no effect. In the stagnation of cold the fall of temperature is the all-sufficient cause, in local syncope it is only the excitant to an already existent nerve disturbance.

The cutaneous symptoms of ergotism may fairly be considered along with this disease, if the anæmia which accompanies ergot poisoning be only spastic and owe nothing to organic causes.

All the above described anæmias, the general as well as the local, may be regarded from one anatomical standpoint, as we are concerned only with a *functional* and not with an *organic* diminution in the size of the vessels. They all (with the exception of the higher degrees of asphyxia) present the same macro- and microscopical appearances.

Macroscopically, the skin is in these cases not altogether white (in Europeans), but has a *yellowish* hue, and, in distinction to the normal, a waxy *transparence*. There is, in addition to the disappearance of some of the red colouring material, some other change in the composition of the skin, and this, I believe, consists in the absence of a large part of the tissue juices; the anæmic skin is drier than the normal. If a piece of skin be thoroughly dried, it becomes yellowish brown and has a horny transparent look, and this yellowish transparence of the skin accompanying the functional contraction of the vessels is the first step of the process. This explains how it is that when anæmia is coupled with pronounced œdema, the skin presents no longer the waxy look seen in syncope, but a more bluish, opaque, milky-white colour. The collagenous tissue is in this case swollen, and not, as in the other, abnormally dry. If the œdema becomes pronounced in particularly thin portions of skin (eyelid, prepuce), the skin becomes again transparent and jelly-like, on account of the presence of fluid in it. A mixture of differently refracting bodies is the more transparent the more one of its components predominates. The colour of the skin of the corpse more nearly resembles the normal than does that of

anæmic skin, for though it presents some of the yellowness of anæmia, it lacks, possibly owing to the rigor mortis, its transparency.

If yet other coloured elements are present, the anæmia acquires various characteristic tinges. The almost complete arrest of the capillary circulation in cholera gives to the bloodless skin its ashy hue. And in "local asphyxia" of the hands and feet, so long as it has not reached its highest degree, the bluish tone of the deep, slowly-flowing blood predominates. In the coloured races, when the blood supply is deficient, the skin becomes still darker. All these frequently-noted facts are also referable to the greater dryness of the skin. For, on the one hand, the epidermis, along with the papillary body, shrinks to a smaller surface, and thus the pigment granules come closer together, and on the other much of the milk-white, strongly refractile character of the collagenous tissue is lost, and on both grounds the dark colour is intensified.

Microscopically, as is easily understood, this form of anæmia presents hardly any differences from that of the normal skin of the corpse. But we must bear in mind that we have in that the appearance of anæmia. The capillaries of the skin and papillary body are shrunk to thin streaks, consisting of rows of endothelial cells, but the larger vessels at the border of the hypoderm are found, on the contrary, in a state of paralysis—viz., fully dilated. In the skin of the corpse, the veins, and often a few venous capillaries, contain blood; the true anæmic skin excised during life should be bloodless. Here, also, if the anæmic skin be skilfully removed and cut with the freezing microtone, an important difference from the skin of the corpse will be found—viz., the large vessels are also found contracted and empty. Further, on every anæmic skin, the papillary body is shrunken, and the lowest epithelial cells have formed into a narrower palisade pattern, so that the deeper inter-epithelial spaces, compared with the more superficial, appear dimished.

Much more interesting discoveries are found in those anæmias of the skin which are caused by organic narrowing of the vessels, of which we have to distinguish two varieties, according as the obliteration comes from *within* or *without* the vessel.

The obliteration of the vessels from without begins in the capillaries and extends to the larger and more resistent vessels. We find it in the neighbourhood of wens, dermoids, larger sebaceous cysts, uric acid concretions, of tumour-like infarctions of the lymph spaces—*e.g.*, lepromata, as the result of pressure in and about scars, and in the striæ gravidarum as the result of strain. The lumen of the capillary loops, mechanically emptied of blood, becomes in time obliterated, and the capillaries become the cellular strings from which they originally

developed. In place of the cellular streaks firm collagenous tissue gradually developes, and thus a part of the vascular system is closed for ever.

The much more common obliteration of the vessels from within, the so-called endarteritis obliterans (Friedländer) begins, on the contrary, in the larger arteries and veins of the hypoderm, and extends outwards to the capillaries. The process can be best observed in the initial sclerosis of syphilis, but the later syphilides, without exception, also tend in the same direction, as do the leprous and tubercular processes, and more or less all chronic inflammatory affections of the skin. Here we have, once more, two classes to indicate—namely, one which tends to *sclerosis of the connective tissue*—scleroderma, keloid, morphoea and the initial sclerosis of syphilis, and another tending to *atrophy*—scars, senile atrophies and atrophies after universal dermatoses (Pityriasis rubra Hebra, Ulerythema, Liodermata, Alopecias). Possibly there is, in addition to the closure of the vessels by growth of the intima, a certain mechanical action, which favours the secondary occlusion of the capillaries, caused in the sclerosis by the pressure of new fibrous tissue, and in the atrophies by the contraction of the scar.

It is the fact that we everywhere meet with this internal obliteration of the vessels in these sclerotic and atrophic processes in the skin, and in these cases we are in the habit of referring the simultaneous occlusion of a great part of the capillaries, to which the white colour of the affected part is due, to the endarteritic and endophlebitic process. But it is equally certain that, in many chronic inflammatory dermatoses (*e.g.*, Lupus, Erythema bullosum vegitans) we meet with a well-marked internal obliteration of the vessels, without having observed during life the faintest trace of anæmia of the skin. This apparent contradiction is, however, simply explained by the fact that in the cases mentioned the process affects only some, never all the larger vessels.

The profuse communication of the capillaries of the skin hinders the occurrence of a circumscribed, avascular area in these cases, just as it does in the not uncommon circumscribed hyalin thromboses, and scattered, harmless infarctions of bacteria in the capillary region; embolism and thrombosis play no part in the etiology of anæmia of the skin.

This experience must make us cautious in attributing the sclerotic and atrophic anæmias to the widespread process of proliferation in the vessels; they are, in all cases, merely mechanical adjuvants. Only where all the larger vessels of an area of the skin are diseased, can we speak of a causal relationship, but certainly in that case, for the process in the arteries produces exactly the same resistance as contraction of

the arteries, which is invariably followed by pallor of the skin, and on account of the permanence of the organic narrowing, a permanent contraction of the less affected vessels must be the result. If, on the contrary, as sometimes occurs, the larger veins of the skin are more affected than the arteries, we must expect, not anæmia, but œdema, as the mechanical effect of the narrowing of the vessels. This narrowing is found in certain chronic inflammatory processes in the skin, which are accompanied by œdema of the cutis, and especially of the papillary body.

B. HYPERÆMIA.

Hyperæmia of the skin may be divided into two distinct classes, *congestive hyperæmia* or *erythema*, and *stagnatory hyperæmia* or *cyanosis*. In contrast to the exciting causes of functional anæmia of the skin, we have in hyperæmia always to do with a paralysis, that is, a diminution of the vessel tone. There is no organic dilation of a vessel, as by the traction of a scar, corresponding to an organic narrowing. But this suspension of the vessel tone is not always distributed equally to all parts of the system; the veins of the skin are, in many cases, not affected, in others they are relatively narrower than the arteries (many angio-neuroses), and in other cases the arteries may be narrowed, while their corresponding veins are widely dilated (certain hypostatic hyperæmias). The dilated vessels always so predominate over the few contracted ones, that one always finds (in specimens excised from the living, and usually on the corpse) longer stretches of the vessels containing blood than on the normal skin. Unfortunately we cannot, on account of the subsequent spastic and mechanical movements, conclude from the situation of the bloody contents what was the seat of the hyperæmia during life; sudden clamping and freezing of the living skin only would make this clear.

In hyperæmia, as in most of the anomalies of circulation, we are largely limited to macroscopic observation. But this, carefully carried out, gives us satisfactory explanations of the ever-changing hyperæmic appearances.

Next we have to distinguish *diffuse* and *areated* hyperæmiæ. We have long clinically distinguished *roseola* from *erythema*. In this distinction we consider not only the absolute size, although there has been an attempt to indicate all distinctly separate erythemas of the size of a pea, a lentil, or a finger-nail, as roseolæ or maculæ. Far more important is it, whether the capillary dilatation affects the superficial vessels of the skin continuously, or in such a way that pre-existing differences in the distribution of the vessels of the skin appear, in other words, have we to do with a *uniform* or a *figured erythema*.

Artificial injections of the skin reach, if moderate pressure be employed, only the directly approachable vascular cones of the skin, whose projection on the surface, in the form of round or oval segments of cones, gives one exactly the impression of a figured roseolate erythema. Only when the pressure is increased, do the spaces remaining between these rings fill up, and there is formed a continuous, connected system of corners and circles. All the segments of the skin surface directly concerned in the to and fro flow of blood I have named "plane elements," the reticular residue between them I have named the "collateral net." In this last we find capillary regions, nourished only indirectly through collateral capillaries. The conjunction of plane elements with the collateral nets forms the continuous capillary track whose profuse filling with blood we describe as uniform erythema.

There is, however, a great number of areate erythemata in which we can trace, externally, no relation to the internal disposition of the vessels—*e.g.*, the infectious erythemata. Around an embolus plugging any capillary, it matters not whether in the centre of a plane element or in a collateral net, a hyperæmic halo is developed—*e.g.*, measles, typhoid. These erythemata have also been named roseola, and they may run together to form diffuse red patches, as in scarlet fever. We see from this, that the areate appearance of the redness is no more a proof that we have to do with circulatory elements than the simple uniformity of any given erythema is against its development from the same, only in certain cases does the development of the exanthem enable us to draw conclusions.

As every single vascular cone of the cutis is surrounded by an elementary circle of collateral net, which, under certain circumstances appears coloured on the skin, so four, eight, or more vascular cones, in connection with a large branch from the hypoderm are again surrounded by a larger ring of the same collateral net. Therefore we see appearing in the figured erythemata, in addition to large and small circular and oval spots, peripheral and central rings, semi-circles, and segments of such.

What, then, is the factor to whose activity such a fundamental difference in the erythemata is to be referred? As the chief difference in the capillary region between plane elements and the collateral net consists in the difference of pressure between them, we are led to think of some regulating factor controlling the tone of the vessels leading to and from the part, in a word, according to the circumstances, on a predominant or absent nerve influence; and, as a fact, almost all the figured erythemata belong to the class of angio-neurosis. But many distinctly traceable to nerve influence (the erythema of anger, chloral and climacteric flushings) are diffuse, and never show any reference to

the plane elements. It is not merely the vague relation to some nerve injury which determines the nature of a figured erythema, but it is a pronounced tendency of all or some of the vessels of the skin, to respond to *definite irritation* such as increased blood pressure, severe cold, toxic infectious influences, and unwontedly *powerful muscular tone.* This abnormal irritability of the vascular system leads either to a simple macular differentiation of the plane elements from the collateral net—*e.g.*, *livedo annularis e frigore*, or it leads further to the characteristic appearances of œdema, to papular swellings and the development of bullæ, which we chiefly observe in one class of the angio-neuroses, the erythanthemata. It causes such severe and characteristic effects, simply through the invariable inco-ordination in the tone of the cutaneous arteries and veins due to the relatively stronger venous tone, which on its part is developed, because the venous radicals are not subjected to the same amount of blood pressure as the arteries. This irrelevant neuropathic restraint of the normal outflow of blood stamps the figured erythemata, as a whole, as stagnatory hyperæmiæ, although the cyanotic character is evinced in very different degree. The simple diffuse or areate erythemata are, on the contrary, mostly congestive hyperæmiæ.

1. Congestive Hyperæmia.

The *congestive hyperæmiæ* or true *erythemata* may be defined as an *excess of blood in the vessels with diminished resistance* and *increased rapidity* of the *blood stream.* This anatomical definition corresponds exactly to the clinical view of congestion, in so far as it combines, in the eyes of the practical physician, the symptoms of increased warmth of the skin and bright red colour. The latter are the natural results of the increased rapidity of the stream, brought about by the removal of the normal resistance. One sees at once that the frequently used synonyms for congestive hyperæmia of the skin, the names "active" or "arterial" hyperæmia, are by no means correct, and they have only helped to perpetuate certain errors. "Active" is certainly not appropriate to the congestion of the cutaneous vessels, for they are paralysed; their idiotonus is in abeyance. And "arterial" is at most the colour of the blood, while the process affects the paralysed veins in as great a degree as the paralysed arteries.

But if we limit ourselves strictly to the simple definition given above, there remains for the erythemata proper a series which is certainly much smaller than that usually given. In particular, according to this definition, many of the erythematous and angio-neurotic inflammations (acute exanthemata, toxic erythemata) are excluded; and further, a number of hyperæmiæ, with diminished rapidity of blood

stream, must be removed and reckoned with the stagnatory hyperæmiæ. We must especially suspect the simple erythematous character of any affection when, in its further course, it developes changes in the epidermis with desquamation, for we know very well that the ordinary (physiological) erythemata never pursue such a course. Our comprehension of simple congestion, as opposed to inflammation, lies in the absence of every secondary tissue change; the simple paralysis of the vessels is sufficient to remove the dangerous irritant. The class of erythemas, as thus limited, comprises some of more general and some of purely local character. The former respond to central or centrally induced irritants, the latter to local ones.

In contrast to the intense, violent, psychical influences, such as fright, anxiety, and fear of death, which have the power of increasing the high tone of the cutaneous vessels to their utmost, and, as a sign of external helplessness, of driving all the blood to the heart from the periphery, the psychical erythemata of tension, joy, shame, and anger are due to much weaker impulses, which suffice to remove the normal tone in the vessel ganglia, and the fulness of blood in the peripheral vessels, thus induced, indicates the commencing reaction of the organism to this weaker irritant.

The most common pathological appearance belonging to this class is the febrile redness, which indicates the reaction to the contraction of all the cutaneous vessels during the rigor, and is the more marked the more intense was the anæmia induced by the cold, and the more the natural tendency to paralysis of the vessels is increased by artificial aids (external heat, warm drinks). All other centrally caused erythemata are more regionally limited, the diffuse prodromal flexure erythema of smallpox,* the group of pure toxic erythemas, especially those caused by atropin, amyl nitrite, and chloral, cause simple hyperæmia, which affects chiefly the head and neck, less the trunk and the joints of the extremities. Certain regionally limited erythemas appear to proceed from certain organs, as circumscribed hyperæmia on the cheeks in phthisis, pneumonia, and the dentition of infants, and more temporary flushings from the female genitals (climacterium, menstruation), and finally in relation to distinct nerve centres and certain peripheral nerves, in hysteria and neuralgia.

The latter lead us on to the erythemata of purely local character, among which we may distinguish physical, chemical, and infectious. We have already noted under anæmia, an idiotonic pressure anæmia of the cutaneous capillaries after slight pressure; for example, after stroking the skin with a lead pencil (the normal autogram of the skin). A

* The roseolous, like prodromal erythemata of variola and vaccinia, belong to the erythanthemata.

fleeting hyperæmia of the affected capillaries usually precedes this more persistent anæmia. But in many perfectly healthy individuals this anæmia is not developed, but we have a hyperæmia which may last a considerable time. In rare cases, and pathologically, this hyperæmia persists, and may still further extend and pass into urticarial œdema (angio-neurotic autogram). More familiar are the pressure hyperæmiæ which are caused by knocks and blows, by repeated irritation, such as scratching, or prolonged pressure, such as is seen after the removal of pieces of cloth and bandages which have remained long on one place. They only rarely go on to inflammation (the inflamed corn and ingrowing nail); the inflammation secondary to scratching is always caused by infection. But it is different in the paralysis of the skin vessels from heat, which begins about 40° C., rises to 50° C., and as the temperature rises, gradually but regularly passes into an inflammatory hyperæmia with œdema, and finally into a burn. Cold also leads, but only indirectly through the reactive tendency of the overcontracted vessel, to congestion, as we see in the fresh red cheeks of the inhabitants of cold climates, and after the application of the ice bag or ether spray. Erythema may also be caused by chemical applications, as in the congestion caused by blisters and liniments, also by the bites of insects, sunburn, and electrolysis; but these also, like the hyperæmias of warmth, if the strength of the irritant be increased, pass insensibly into true inflammation.

Related to these chemically induced congestions are certain infectious exanthems, which we can definitely recognise as due to a chemical, locally active poison, produced by a specific germ. Such are the roseola-like spots in typhoid, typhus, dysentery, diphtheria, and pneumonia, recurrent fever, acute rheumatism, and influenza. It is very probable that here there is no centrally induced paralysis of the vessels. On the other hand, there is nothing in common with the angio-neurotic disturbances seen in the cholera rash and the early vaccinal rash. These roseolæ are rather to be considered simply as areas of reaction, around more or less scattered emboli of the specific germ, and performing the functions of "undertakers" to these germs, a circumstance which is not favourable to the cultivation of the latter from these rapidly transient spots. But whether in all these cases we have to do only with the simple paralysis of the vessels, or with a slight degree of inflammation, remains to be decided.

That the anatomical observations in hyperæmia, after excision from the living or the dead, are very meagre and of little utility, has already been stated. This is chiefly due to the fact that in pure erythema, except for the functional weakness of the vessel muscles, which, in death or excision, is usually removed, there are no further changes; the stag-

natory hyperæmias leave, as we shall see, more marked traces of their existence.

In life, every congestive hyperæmia is characterised by increased warmth and redness of the surface, the more intensely developed is the latter, the darker and bluer it appears, not, as has been suggested, because every "arterial" hyperæmia passes into a more "venous" one, but because in more marked congestion the deeper-lying veins and arteries of the skin are more filled, and then appear bluish, through the lighter red of the superficial vessels. Even in long-standing pure erythemas, there is no œdema and no pigmentation. Dilatation of the lymph spaces, and accumulation of pigment in the cutis, always indicate therefore the complication of stagnatory congestion.

2. Stagnatory Hyperæmia.

Stagnatory hyperæmia or cyanosis may be simply and clearly defined, it is *an over-filling of the skin vessels* with *increased resistance* and *diminished speed of the stream.* To these is due the coldness and the bluish red colour of the skin. Œdema and hæmorrhage are often developed, and as the congestive hyperæmias may pass into inflammation, so the stagnatory hyperæmias terminate, not infrequently, in necrosis.

Here also we must protest against the frequently used name of "passive" or "venous" hyperæmia, for, on the one hand, the restraints which locally lead to congestion are often, indeed usually, founded in full activity of the vessel walls, and, on the other, the stagnating blood, in many cases, fills up the arteries as well as the veins. Therefore the name stagnatory hyperæmia corresponds both to the clinical symptoms and the anatomical appearances. In congestive hyperæmia only the in-flow of blood is increased, in stagnatory hyperæmia the out-flow is made more difficult. But while in the former the anatomical conditions are uniform in nature, consisting in a paralysis of the vasomotors, in the group of cyanoses they are as different as possible. Sometimes they appear as manifestations of general stagnation, sometimes they are locally induced by central resistance to the out-flow of blood in the veins or in the arteries and veins (influence of cold), or finally in the capillary region itself (removal of atmospheric pressure). Consequently the accompanying conditions and especially the anatomical results are very different, and each must be discussed by itself.

Simplest and most like the congestive hyperæmias are the conditions in those general stagnations, which, partly acutely, as a result of suspension of respiration (choking, hanging, asphyxia of new-born children, in chloroform poisoning, paroxysms of coughing), partly

chronically, in organic heart and lung diseases, are evident as cyanosis. Here we have to do with a simultaneous flooding of the whole vascular system, as in erythema; only the dilatation in cyanosis begins at the venous end, and gradually reaches the beginnings of the arteries, and the accompanying paresis is not induced from the ganglia outside the vessels, but from the vessel contents. It is owing to this latter circumstance—*i.e.*, the mechanical pressure paralysis of the vessel muscles, that in all long standing cyanoses, even after excision and on the corpse, the dilatation of the vessels, and especially of the capillaries, can always be recognised, although in the latter case it is augmented by the post-mortem lividity. In addition one must not forget that in all dyspnoeics, in addition to the mechanical cause of the blood stagnation in the skin, there is also brought about, through the suspension of respiration, a central paralytic hyperæmia (Heidenhain).

General cyanotics do not show the same bluish red colour equally in all parts of the skin, but only those parts present the characteristic colour which, by their exposed situation, are the seats of physiological congestion, especially the face (including the ears), the hands, feet, elbows, &c. The backward stagnation is only pronounced where the arterial and venous tone of the skin is normally weak and the capillary region consequently relatively open.

Still more circumscribed are the cyanotic areas, if the causes of general stagnation are found in the arterial circulation, when, from fatty heart, arterial sclerosis, patches in the heart muscle, &c., the blood pressure, as well as the rapidity of the stream, is materially diminished. Then there appears on the pointed ends of the body, the nose, the ears, the fingers, and the toes, under the influence of the great loss of heat, a regulatory higher tone of the arteries and veins, which limits and slows the blood stream. These regions of the skin, which are normally of a fresh red colour from physiological congestion, then assume the well-known ominous blue colour, which, with warmth, returns to the colour of congestion. The special tendency of the pointed extremities to the most different forms of cyanosis we will often meet. One may group all these forms under the term Acrocyanosis. Owing to the better tone of the cutaneous vessels in these cases, we find, post-mortem, little trace of the dilatation.

The appearances are quite different in the local stagnatory hyperæmias. A very instructive form is the acute compression hyperæmia, which we can produce by bandaging the arm, as if for bleeding.* After the first very evident swelling of the chief veins, this disappears in a general but relatively slight swelling of the whole

* See Auspitz on Venous Stagnation in the Skin. A. A., 1874, p. 275.

arm. This is greyish blue or ashy grey, dotted with vermilion red. In typical cases these red spots are seen to be the plane elements, which are surrounded by grey blue collateral nets. Where there is greater stagnation, the red colour extends diffusely over the arm, and there appear here and there spots sometimes white and quite anæmic, sometimes red or bluish black. This indicates that the larger veins, both in their own expansion and in the capillary region, interpose a strong spastic resistance which, by extension to the arterial regions, may even lead at certain points to anæmia. The bright red spots indicate the escape of serum, containing hæmoglobin, the blue and red points, the superficial or deeper lying escapes of red corpuscles.

As the result of the whole process, which stands between stagnatory hyperæmia and spastic anæmia, there remain, at the seat of the escaped hæmoglobin, pale brown pigmented areas, while the small diapedetic petechiæ go through the ordinary play of colours.

Compression hyperæmiæ, which develope more slowly, show only very rarely, for example on the leg, spastic narrowing of the veins, but lead directly to venous dilatation. Especially on the legs during pregnancy, one can observe the successive swelling, first of the large veins in the form of blue or bluish black deep-lying lines, then of the smaller cutaneous veins in the form of carmin red, branching and freely communicating twigs, and finally in very severe cases, the capillaries as a general bluish redness along with œdematous swelling. In such cases the veins, especially before the valves, are vermicularly dilated, and here usually lose for ever, from the pregnancy, a part of their contractility—the most frequent cause of the formation of varix. The gravid uterus compresses equally all the veins of the leg, and only thus is such a weak compression able to induce such severe stagnation. For the rich anastomotic connection of all veins favours the fact that even a slight pressure on all the veins of the region leads to stagnation. So there develope stagnations of the arm from tumours of the axilla, of the leg from pelvic tumours, of the abdominal veins (Caput Medusæ) in compression of all the portal veins from cirrhosis of the liver, of the veins penetrating the muscles of the thoracic exit in increased activity of these muscles, on the head of newborn children by pressure on the whole periphery of the head. Single, although complete stoppages of the venous stream, like large thrombi, calcareous concretions, or operation scars never induce a venous stagnation but only a transference, a deviation of the normal course of the venous blood.

There are also under the local stagnation hyperæmias, some in which the hindrance comes from the vessel contents. The removal of

the atmospheric pressure by a bleeding cup causes first a fixation of the blood and the lymph in the tissues. While the arterial blood bursts into the too weakly supported surroundings, the venous blood is sucked out and the freely transuding lymph retained in the tissues. There is thus brought about by this simple agent, in a very short time, the highest degree of stagnation, of watery and bloody œdema; and later we get stasis, the formation of blood-containing vesicles and necrosis. If the cupping does not go the length of causing stasis, the stagnation rapidly passes, the œdema disappears, and there remain only the diapedetic hæmorrhages, which are slowly decolourised.

A similar collection of the blood, from both sides of the vessels in the capillary region, is found as an artificial change in all pieces of skin (tumours) removed by slow snaring, and in a lesser degree by the snip of the scissors, and must not lead one to assume that there was marked hyperæmia in the living tissues. This artificial production of hyperæmia can be recognised by the fact that only the most superficial capillaries are dilated with blood, and that this dilation diminishes rapidly deeper down.

The *hypostatic hyperæmias* form yet another group of the stagnatory hyperæmias. Here also, as in the last-named cyanosis, we have to do with a backward movement of the venous blood, but at the same time the *Vis a tergo*, the arterial blood pressure, is much diminished or entirely removed, so that the fulness of the capillary region is much less than in cupping. The impulse to backward movement of the venous blood is always favoured by gravity, as is well seen after death during the disappearance of the rigor mortis, when the blood from the larger venous trunks, obeying the laws of gravity, sinks back into the dependent capillary regions, from which it was pressed during the death agony. We have already seen that a favouring factor for the formation of post-mortem lividity exists in all paralyses of vessels existing during life, in circumscribed pressure paralysis, just as in general cyanosis. In this last, the agonal anæmia is often not developed, and the cyanosis of the living passes in many cases directly into post-mortem lividity.

Hypostatic hyperæmias are found during life in weakened bed-ridden persons, and in convalescents after long illnesses, for the aspiration of the lungs, the driving power of the heart, muscular movements, in short, every impulse to the onward movement of the venous blood is here largely in abeyance. On the back, the sacrum, the buttocks, and heels there is added, when the body is raised to the normal congestive hyperæmia, a hypostatic hyperæmia. Thus the otherwise salutary compensation of the congestive hyperæmia is paralysed, the pressed skin is, neither during the time of the pressure anæmia nor

during the intercurrent period of stagnation, properly nourished, and necrosis gradually supervenes (decubitus).

We observe hypostatic hyperæmia most commonly on the legs of those persons whose profession compels them to stand constantly, in men more rarely than in women, in whom the compression stagnation of pregnancy is often added. In particular the vessels of the skin of the leg, in lesser degree of the ankle and knee joint, and rarely of the foot and thigh, present a series of characteristic changes, which are by no means so simple as usually supposed. Gravity undoubtedly acts on the blood column in the arteries increasing the pressure just as in the veins, accelerating the one, delaying the other. It alone brings about a similar condition of over-filling in the capillaries, particularly in the feet as, in much higher degree, does the cupping glass. To the first, usually transient *period of muscular insufficiency* of the vessels, there rapidly succeeds a second *period of compensation,* in which the earlier difficulties are completely overcome. The heightening of the tone of the arteries as well as that of the veins brings on this compensation in the simplest manner, but not of course without at the same time markedly increasing the resistance to the whole circulation of the leg. And on this point depend all those later symptoms of disturbed compensation, which, as varix and ulcer of the leg, are so familiar. The much diminished "Vis a tergo" allows the blood of the large veins to sink as far as the valves of the subcutaneous veins of the legs. The stagnation in this *third period,* when cases usually come for treatment, is consequently, from its development, a hypostatic hyperæmia. Therefore the centrally lying parts of the dilated venous trunks are swollen by pressure on them (Trendelenburg), and not the peripheral, as in ordinary stagnation hyperæmia. Next the valves are distorted, the veins above them dilated and twisted through stretching. At the seat of the valves there are formed, with disappearance of the muscular and elastic coats, sack-like dilatations; the varices. At this stage the process may long remain stationary; and even by limited coagulation in the varix, and consequent organisation or caseation, lead to a diminution of the open venous canal, and thus to relative recovery. On the other hand under favourable circumstances, or with artificial aid (constant compression), the dilated venous walls may be strengthened by the formation of new fibrous tissue, and the results of hypostatic hyperæmia on the leg partly compensated. But there developes, in a large number of cases, in addition to an *insufficiency, an organic resistance,* supplied by the valves and the hypertrophied walls of the varicose veins, and now ensues a capillary stasis in the whole under extremity, or certain cutaneous areas—*the fourth period.* There are certain weak points of this region, where the results of the permanent stagnation are

already apparent, such as the skin over the anterior surface of the tibia and around the malleoli. The mildest form is a simple pigmentation, sometimes in the form of spots, sometimes more diffuse, here and there forming regular marbling, according to the size of the plane elements; more marked pigmentation is only present after long standing stagnation in the absence of œdema. The weaker the arterial tone of the extremities, the earlier does a more general or more circumscribed œdema appear; in slight cases only in the neighbourhood of the ankle joint; in these cases the diapedetic phenomena tend to be less pronounced. In the fourth period of complete insufficiency, we have circumscribed, shilling to crown piece-sized areas of marked hyperæmia, going on to œdema. Owing to the capillary dilatation and the bloody œdema, these spots are coloured dark bluish red to black, and are soft and painful to the touch. A slight injury of the epidermis, such as a blow, is now sufficient to bring about the almost immediate destruction of the spot and the formation of a very slowly healing ulcer of the leg. This is the commonest way in which these ulcers begin. Eczema of the leg is another cause, brought about by scratching the itching, congested skin. There then appears a combination of the eczematous inflammation and congestion, a destruction of the upper layers of the skin not seen in eczema alone, usually commencing at the seat of the deeper scratches, which refuse to heal.* If larger veins with thinned walls are implicated, there is a great tendency to severe hæmorrhage, which, in spite of its venous character, is very difficult to arrest, for the surroundings of the vessels have entirely lost their elasticity.

We have already several times indicated the close relationships between stagnatory hyperæmia and anæmia. The reason of this is that in both, the resistance in the capillary region is abnormally great; only the amount of blood is different. Therefore it is that in many cases the two conditions pass into one another, as, at certain points of the cutaneous circulation, resistance is increased or diminished.

When a simple anæmia of cold induces, by a certain degree of injury of the endothelial nerves, a salutary congestive hyperæmia, and by the assistance of the regulatory vasomotor apparatus, all previous resistance is suddenly removed, there cannot be between these conditions any simple relation. In the one the skin is exposed to the ever-narrowing circle of vessel contraction brought about by cold and deficiency of blood, which leads to freezing; in the other it is distended with blood, and thus removed from the influence of cold. But quite other conditions are seen, if there already exist normally in the skin a slight degree of stagnation caused by a somewhat elevated venous tone. Such is found in many young emaciated individuals, especially

* For other causes see under ulcus cruris.

on the limbs. If such persons are exposed to a moderate amount of cold, as in dressing in a cold room or a cold bath, there is observed a regularly arranged marbling, corresponding to the plane elements, which, contracting more strongly, show out white, against the blue grey, or, in the case of severe stagnation, red spotted background of collateral net. In this "livedo annularis e frigore," we have a half-way house between the simple anæmia of cold and the simple diffuse cyanosis of cold (Livedo diffusa) which, as the expression of a simply delayed peripheral circulation, is often enough seen.

This slight, almost physiological, change of an increased venous tone in livedo annularis, brings us to the consideration of chilblains (Perniosis), and thus into the region of the angio-neuroses which, except for their anæmic manifestations, should certainly be enrolled in the chapter of stagnatory hyperæmia. For here we have to do, as the name indicates, with a more or less marked participation of the vessel tone. But this is incompatible with the paralytic hyperæmias of congestion. The near relationship of stagnatory hyperæmia to anæmia is shown even in this last group, for the angio-neurotic anæmias and angio-neurotic cyanoses can pass directly the one into the other. To the local syncope of the hands and feet correspond, not only, under the angio-neurotic cyanoses, the complex symptoms of chilblain, there is also a special condition of the ends of the extremities which is described as "local asphyxia" (Raynaud) or "regional cyanosis" (Weiss), which we may look upon as an intermediate condition between local syncope and Perniosis (chilblain). The following little table explains the relationships of the anomalies of vessel tone to the combinations of symptoms :—

	Local Syncope.	Local Asphyxia.	Perniosis. (Advanced Degree).
Venous Tone.	Very high.	Very high.	Very high.
Arterial Tone.	Very high.	Higher than normal, but relatively weak compared to the venous tone.	Normal or very low.
1. Anæmia.	Very pronounced.	Present in areas	Absent.
2. Cyanosis.	Absent.	Preponderates.	Very pronounced.
3. Temperature.	Always lowered.	Irregularly lowered.	Only sometimes lowered.
4. Subjective Symptoms.	Absent or very slight.	Sometimes present.	Always marked.
5. Swelling.	Absent.	Present in areas.	Always present.
6. Vermilion red spots.	Absent.	Occur.	Always present.
7. Chilblains.	Absent.	Absent.	Always present.
8. Necrosis.	Appears painlessly in small areas.	Affects large areas, is painful, and goes on to mummification.	Absent.

Hands and feet affected with chilblains show, even in warm weather, an abnormal vascular tone, viz., a relatively strong venous tone, and, therefore, a bluish, unhealthy colour, a cold, clammy surface, and a tendency to the appearance of vermilion red spots. But it is in the cold that the signs of stagnation are first distinctly prominent. There developes then, on account of the relatively weak arterial tone, not a beneficial congestive hyperæmia as on healthy skin, but only an increase of the tone. Where more active cold produces an arterial paralysis, it leads only to the appearance of a severely itching, bloody œdema, a chilblain. So that perniosis is a distinct acro-cyanosis. It can only affect the ends of the extremities, for there only are the effects of the stagnation of cold not compensated through collateral paths. In rare cases the point of the nose along with the hands and feet, or even without them, is the seat of a perniosis, a bluish congestive redness. These are the rare cases in which one may correctly speak of a true *angio-neurotic rosacea.* The ordinary cases of rosacea are seborrhœic and inflammatory. Chilblain is in no sense a freezing of the skin, and perniosis has up to now been everywhere wrongly ranked along with frost bite. Its place is with the " angio-neuroses," by which we understand such disturbances of the circulation as are *characterised by very great muscular irritability of the cutaneous vessels,* and which we shall consider more closely in the next chapter.

C. ANGIO-NEUROSES.

By angio-neuroses of the skin we understand a large group of skin eruptions which clinically present marked differences, but which all owe their origin to an *excessive irritability of the muscle tone* of the *cutaneous vessels.* In addition to the most important general irritants which are the possible causes of these eruptions—variations of the blood pressure and external temperature—there is a large number of special irritants which only call forth definite forms of the exanthem in definite individuals, a relationship between irritant and individual which we call an idiosyncrasy. The exanthem has a course synchronous with the irritant, and as this in most cases acts acutely, it has in general a fleeting character. But there are chronic exanthems of this form, in which continual irritation of an unknown nature must be assumed (perniosis, urticaria communis chronica, Quincke's œdema). In all cases we have a symmetrical distribution of the angiogenic habit, and usually the eruption is related to the circulatory plane elements of the skin, especially where it assumes the form of roseola, papular erythema, wheals, nodules, vesicles, and bullæ; less so, where diffuse anæmia and hyperæmia are induced. According to the greater or less implication of individual sections of the vascular system the angio-neurotic ex-

anthemata may be subdivided into anæmias, cyanoses, œdemas, and erythanthemata. Whether there are angio-neurotic hæmorrhages is still doubtful. As a functional disturbance of the muscle tone is the mainspring of the angio-neuroses, our pathologico-anatomical knowledge of it is in general much less than our clinical. Only in the most severe and persistent cases are marked histological changes discernible, as in bullous erythanthema. The majority show, so far as any histological alterations are visible, a very uniform anatomical framework—hypertrophic changes around the blood-vessels and dilatation of the lymphatics—by no means corresponding to the great variety of the clinical appearances.

We must further at once separate from the pure angio-neuroses of the skin certain well defined dermatoses, which up to now have been considered with them; the true Erythema multiforme of Hebra and Erythema nodosum. These, with the neuroleprides and neurosyphilides, form a definite, most interesting, little group of infectious inflammations of the skin, which, in certain angio-neurotic symptoms, have certainly a superficial resemblance to the true angio-neuroses. But in them there are, owing to the specific infectious irritant, histological changes in the texture of the skin which are absent in the simple angio-neuroses.

As the anæmic and cyanotic angio-neuroses have already been treated of in the chapters on anæmia and stagnation hyperæmia, we consider in this, specially, only the œdematous angio-neuroses and the erythanthemata.

1. Angio-neurotic Œdema.

The great majority of all angio-neuroses of the skin is complicated with more or less spastic œdema. Nevertheless we consider under this heading only a small group of cases, comprising just two definitely defined diseases, *Acute circumscribed œdema* (Quincke's œdema) and the so-called *Urticaria factitia.* These are the only dermatoses in which the angio-neurotic œdema predominates over all other symptoms, and in which in particular a papular erythema, connected with the circulatory plane elements of the skin, does not form the basis of the œdema. For where this last is the case—as in most forms of urticaria—the chief interest is so concentrated around these circulatory elements that one is tempted to slump all the appearances together, and to treat them all under one common name, erythanthema.

Quincke's acute circumscribed œdema must, however, not be reckoned with the erythanthemata, for the simple anatomical reason that not only the cutis but the hypoderm also is affected, and that its limitation is not that of the superficial circulatory elements nor

of a group of them. It is manifest that it is in the larger cutaneous branches coming through the muscles and fascia, that the abnormal irritant phenomena take place, and the accompanying œdema of the skin plays only an unimportant role, compared with the subcutaneous œdema, which raises the skin into nodules as large as an apple. A preliminary hyperæmia of the hypoderm, preceding the spastic œdema, cannot usually be determined, and thus each lesion runs its course as a simple immovable, not plastic but elastic, circumscribed œdema.

There is, however, no doubt that an intimate relationship exists between these cases and the papular erythanthemata, and under that last heading I have more definitely described (see below), to illustrate this relationship, a case of gradual transformation of a Quincke's œdema into a true papular erythanthema of the skin. But there is a further distinction than the different points of attack of the irritant—viz., that this "giant urticaria" (Milton) almost never, the papular erythanthema almost always, appears symmetrically. The rough analogy of the two processes is most useful, for, up to now, there has been no histological examination of Quincke's œdema. We can surely not go far wrong in filling up, temporarily, this defect from our anatomical observations of papular and urticarial erythanthema (see these). We are more fortunate in connection with the so-called *Urticaria factitia*. Here also we cannot look for the starting point of the œdema in the circulatory elements, for we can induce the œdema when and where we will. We must rather ascribe to the whole surface of the skin the power to respond to an adequate irritant, external pressure, with an œdema exactly in the seat of the pressure. Were we able from a simple point, as by irritation with the sting of a gnat or a nettle hair, to cause œdema of a whole vascular cone, which we are not, then only would urticaria factitia belong to the true erythanthemata. The connection with the pressed surface of the skin and the want of connection with the disturbed circulatory plane elements, shows that here the adequate irritant must act on parts of the vascular system and its nerves other than in the erythanthemata, in spite of the external resemblances of the eruptions.

It is histologically of the greatest interest to investigate the differences in the irritated and unirritated skin of those disposed to urticaria factitia. Several artificially-induced wheals from a typical case in my hospital gave the following corroborative results.

The skin, as well as the papillary body, was moderately swollen, in consequence of an interstitial œdema of all the lymph spaces of the skin. The larger lymph vessels were likewise dilated and appeared in some sections as broad endothelial-lined, fibrin-containing canals. Here I should like to refer to a not very striking, but when observed

infallible, sign of œdema of the lymph spaces of the skin, which is of especial importance in the erythanthemata. It is not always easy, and more difficult the finer the section is, to distinguish between interstitial œdema of the skin and cracks in the section artificially caused by pressure. If the œdema is not marked, there is no dilatation of the lymph vessels, and one will often, unwittingly, overlook an existent œdema. The indication is this: every œdema of the lymph spaces separates the elastic fibres. Wherever we observe an elastic fibre stretched across an opening in the tissue in a different direction to the neighbouring fibres, that space was present in life, for the elastic fibres cut through in section separate from each other, when the section is pressed, in a direction always parallel to the collagenous bundles.

This is seen particularly on thicker sections which do not so readily admit of subsequent dislocation of the collagenous tissue. Slighter degrees of œdema of the skin can only be detected in thicker sections which have received a good elastic and collagenous stain (acid orcein).

In addition to the general dilatation of the lymph vessels of the cutis, there is a change in the blood vessels which, in different degrees of development, is met with in all erythanthemata.

The vessel walls are richer than usual in simple spindle connective tissue cells. These, as well as their nuclei, are more voluminous than normal, and the collagenous intercellular substance is thickened and stains more deeply. The increase in size and number of the fixed cells reaches a few cell breadths from the vessel into the cutis, so that the smallest arteries and veins, instead of tending to the capillary type, have an adventitia one or two cells broad. Inside these last we find mast cells pretty regularly arranged. These, as usual in acute processes, are small and round, but whether they have wandered in, or have developed from fixed cells locally, must be left undecided. One or two mitoses in the inside of these vessels complete the picture.

We have then a general hyperplastic condition of the cutaneous vessels. This hyperplasia accompanies all angio-neuroses of the skin which are associated with long-standing arterial hyperæmia, it is a sign of the hyper-nutrition and indicates the functional irritation of the vessel walls, which lies at the bottom of this, as of all angio-neuroses.

A third never-failing symptom is the presence of mitosis of the basal prickle layer. The quantity of these certainly varies and depends on the varying development of the hyperæmia and œdema of the papillæ. But here and there we come across areas which swarm with epithelial mitosis such as are usually seen only in rapidly-growing tumours. This observation separates urticaria factitia from other urticarias, and

may very well depend on the application of the irritant through the epithelium.

Finally, we find, in the older layers of prickle cells, a moderate œdema, dilatation of the nuclear cavities and a moderate dilatation of the lymph spaces of the epithelium.

In distinction to these observations, a piece of skin from the back of the same patient, which for months, at least, had not been irritated, showed: first, no interstitial œdema of the cutis, no œdema of the papillary body and the prickle layer, and no mitosis. But the vessels showed, though not so markedly, the same appearances of hyperplasia, especially when contrasted with the dorsal skin of a healthy person. The fixed cells of the vessel walls were increased in number, they were less voluminous than those on the irritated spot, and mast-cells were present in an amount much greater than normal.

Are these abnormal appearances in the vessels of the unirritated skin possibly the objective signs of a disposition to urticaria factitia and its necessary basis? Without very numerous additional examinations of unirritated skin from such subjects, this important question cannot be definitely decided. But even an invariably positive result would not prove that a chronic "irritated" cellular vascular system of the skin was necessary to the production of the urticarial autogram. For the certainty that no unintentional irritation had taken place on the piece examined is never absolute.

But otherwise there is much against considering this symptom as the necessary basis of Urticaria factitia. For one thing the clinical experience, that the phenomenon can as easily be induced on unirritated skin, as on that which has been recently irritated, in which the vessel hyperplasia is certainly greater, teaches us that there is no increase in the effect through repeated irritation. Therefore the hyperplasia of the vessels, even supposing it to be found on all, as yet, unirritated spots, would still not explain the possibility of functional irritation. For that, some alteration of the nervous system of the skin vessels alone is sufficient, and their examination is as yet beyond our power. I prefer, then, to recognise, in the slight hyperplasia of the "unirritated" skin, nothing more than the persistent remains of an earlier, unnoticed, transient irritation, whose existence on the outer skin can never be altogether excluded.

2. Erythanthema (*Auspitz-Unna*).

The most interesting division of the angio-neuroses comprises eruptions whose initial form is maculo-papular, and in which the form of the single lesions and their grouping, leaves no doubt as to their connection with the circulatory plane elements of the skin. They

show a further development of this fundamental type in two directions. Either the epidermis is affected and is raised into vesicles and bullæ, or the process terminates in a circumscribed severe œdema of the skin, in wheal formation. On account of the bullous development of this form of exanthem, it is usually, but wrongly, considered as related to pemphigus or to the vasicular developement of Erythema multiforme; Herpes iris. The wheal-formed erythanthemata on the contrary, since they have fewer individual varieties, have for a long time borne a special name; Urticaria.

The various forms of urticaria form * however with the angioneuroses of maculo-papular ground type, with or without bullous development, a well-defined group to which, in view of its fundamental type, I have given Auspitz's name of *Erythanthema.* Especially in their case, we must avoid any confusion with Erythema multiforme (Hebra) (see above under angioneurosis) and bullous neurotic dermatitis (Hydroa).

According as the erythanthemata appear as the result or the symptoms of other disturbances or as independent chronic diseases, we must distinguish symptomatic and idiopathic. To the first belong the larger groups of reflex, toxic and infectious erythanthemata. The reflex are mostly brought about by affections of the female, more rarely of the male genitals, by heart affections, irritation of the peritoneum, by dentition or finally by hypersensitive taste and smell. The toxic erythanthemata are either local in their nature (stings of nettles and insects) or universally distributed (all angioneurotic drug eruptions). An example of the infectious erythanthemata, is the rash which precedes the outbreak of small-pox.

Still more interesting and important, although as yet without a definite place in our system, are the idiopathic (or essential) erythanthemata of papular, bullous or urticarial form, of which only the last have won their own place as forms of urticaria.

(*a*) Symptomatic Erythanthema.

As examples of the symptomatic erythanthemata, we will describe two from the toxic group, a local Urticaria traumatica caused by nettles and a papular erythanthema which appeared after an injection of tuberculin.

Urticaria traumatica caused by nettles.

A wheal excised from the arm of an adult immediately after its induction showed appearances of the most acute spastic œdema. All

* With the exception of Urticaria Factitia, which it would be better to call "urticarial Autogram."

hypertrophic changes of the blood vessels and especially of the papillary capillaries were absent, there were neither œdematous changes nor mitoses of the epithelium. The only histological change, which is certainly sufficient to explain all the clinical appearances, concerns all the lymph vessels and spaces of the deeper and middle layers of the skin. These were enormously dilated, so that the blood vessels, nerves, and sweat ducts of the region stood out prominently. The tubular cavities of the lymph vessels appear in longitudinal section as broad canals, in cross section, as sharply margined cavities lined with endothelium. The dilated lymph spaces are best seen on thick sections with good collagenous staining, as irregular, sometimes round and then sharply contoured, sometimes with sacular processes when they appear as margined spaces in the collagenous tissue. The rapid forcible dilatation of these pre-existing lymph channels is evidenced in the irregular course of the over-stretched, frequently torn elastic fibres, here and there crowded together into bundles.

FIG. 1. Urticaria caused by nettle sting.
Wide lymph spaces in the lower and middle cutis and around the vessels, ducts, &c.
The wavy black lines are the elastic fibres.

The dilatation of the lymph canals culminates at the lower border of the cutis in the neighbourhood of the deep vascular net, but is still very evident in the middle of the cutis, especially around the ascending branches of the vessels; it is gradually lost in the papillary body. This is, as a whole, somewhat œdematous without showing any large spaces; the epithelium is, on account of this slight œdema, correspond-

ingly stretched, the ridge net is slightly thinned. The stagnation of blood which leads to œdema evidently begins around the larger veins and extends backwards towards the papillary body. It causes the compression of a great part of the blood capillaries, and thus induces the milk-white pallor of the irritated skin. There has been no time for a reactive cell growth of the blood vessels irritated by the juice of the nettle. Other symptoms of inflammation are absent, especially all leucocytes. We have to do with a pure, very *acutely* appearing, spastic œdema.

Erythanthema toxicum papulosum, following the injection of Tuberculin.

This was a universal eruption, which appeared in a child along with the other symptoms of tuberculin injection, and disappeared spontaneously. It had the form of a papular erythema of wheal-like form, somewhat comparable to lichen urticatus.

The chief symptom, here as in the former case, was a widespread œdema of the lymph spaces of the cutis. But the larger lymph vessels were less dilated, and the dilation of the spaces extended pretty equally from the hypoderm to the papillary body.

The numerous hair follicles, muscles, and coil glands of the skin were all surrounded by wide lymph spaces. But these last were only rarely separated from the collagenous tissue by a sharp margin, more generally they pressed it irregularly aside and sent processes between its fibres. The blood vessels were rather more cellular than normal; particularly striking were the regularly distributed mast cells around them, here and there they were arranged in clumps around the hair follicles and in such numbers that they might be definitely looked upon as abnormal. A few of them, quite independent of the blood vessels, were scattered in the collagenous tissue. The elastic tissue is normal and mechanically stretched as it passes over some dilated lymph spaces. The papillæ show no large spaces, but are, on the whole, distinctly swollen. The epithelial ridges which sink down between them are consequently not merely stretched and thinned, but even of abnormal breadth. The increase in volume is mainly owing to a general œdema of the older epithelial layers, which is shown as a perinuclear œdema, to a dilatation of all the nuclear cavities, and in a lesser degree to mitotic new formation of the basal prickle layer.

This exanthem represents a sub-acute spastic œdema of moderate tension and equal distribution over all the capillary lymphatics. This is complicated with hyperæmia, commencing cell proliferation round the blood vessels, accumulation of mast cells and slight œdema of the older, and mitotic formation of the younger prickle cells.

(*b*) Idiopathic Erythanthema.

In this group we have to do with chronic dermatoses in which continuous eruptions, of the type of erythanthema, appear and disappear without any other apparent cause than a peculiar disposition of the skin. In some cases the disease begins with definite intoxications; but these are merely to be considered as predisposing and not as sufficiently exciting causes, for after the disappearance of the intoxication, the disease of the skin persists. This disposition of the skin shows itself histologically, at the height of the disease, in that complication of symptoms, common to most angioneuroses, an "irritable" cellular vessel wall and a very varying amount of œdema. A question more difficult to decide is whether this existing structural change is at the bottom of the constant recurrence of the process or if it is, so far as that is concerned, irrelevant, and rather to be considered only as a harmless residuum, an indication of a bygone eruption. This question has already been discussed in relation to the analogous case of so-called Urticaria factitia: the persistent signs of irritation are probably not to be regarded as representing a disposition lying at the root of the whole disease. But in this form of erythema there are more serious disturbances of the structure of the skin, and these can certainly not be held innocent of the eruption. Thus I have no doubt that the mucous softening of the papillary body in the case of erythanthema bullosum, afterwards described, must have aided the constant new formation of bullæ. As to the commencement of the formation of the eruption and the question, why in a given case the bullæ usually appear symmetrically and not on other areas also, I prefer to conclude, as in urticaria factitia, that the histological basis is not yet discovered and still lies buried in the black obscurity of vessel nerve alteration. But it is by no means excluded that, granting the disposition, external injuries, especially pressure, may as easily be the direct cause of the eruption as nervous irritants from within.

The further sub-division of the idiopathic erythanthemata can only be by means of the coarse clinical landmarks of the presence or absence of bullæ and wheal formation. This is, of course, also an anatomical division. I distinguish three groups: the maculo-papular, the papulo-bullous, and the urticarial.

Maculo-papular Form.

The cases belonging to this class have hitherto been described as remarkable examples of chronic or universal Erythema multiforme (Hebra) as Urticaria rubra, or as Lichen urticatus. No case exactly

resembles another, but in spite of individual differences, they all have the stamp of a maculo-papular idiopathic erythanthema.

Case D.—A. This is of especial interest as it began as a true Quincke's œdema with nodules, neither red nor tender. They varied in size from a nut to an apple, appeared suddenly and disappeared slowly, reached into the cutis, but were mainly subcutaneous. After a long period of observation the case developed into a tubero-papular, and finally into a typically papular erythanthema. The eruption then had the form of circular, ringed or gyrate papular erythema. This case represented the bond between idiopathic erythanthema and angioneurotic œdema, especially Quincke's, and this last passes anatomically from the domain of the erythanthemata only through its affecting subcutaneous regions; clinically it certainly belongs to the same group.

A papule, limited to the skin, was excised in the last stage of the disease. Even with the naked eye, large round and cylindrical holes could be seen in the sections, definitely defining the border of the cutis proper, from the markedly swollen papillary body. The microscope showed that we had to do with widely dilated lymphatic vessels accompanying the subpapillary vascular net. The endothelial lining was everywhere evident, but there were no mitoses. It is remarkable that neither into the papillary body nor downwards into the cutis do processes of these fully dilated lymph vessels extend. Only here and there are there round holes of distinctly lesser calibre, and in general the lymph spaces are only slightly, the lymph vessels not at all, dilated. But, on the other hand, the papillary body, as already mentioned, shows a general swelling, which is to be referred only partly to the moderate dilatation of its lymph spaces, for the most part, to a peculiar dropsical character of the collagenous tissue of which it is composed. With many stains, which stain this swollen tissue more deeply than the normal collagenous tissue of the cutis, the papillary body, as a whole, is defined unusually sharply from the remaining cutis, and the margins of both are formed by the large lymphatic plexus.

The blood-vessels in the upper half of the cutis and in the papillæ show definite increase of the cells, but not those in the neighbourhood of the deep plexus. The epithelial ridge net is stretched and thinned. The prickle layer shows no mitosis, but slight œdematous changes in the form of dilated nuclear cavities.

This type of œdema is, in the enormous dilatation of the subpapillary lymph vessels and the consequent swelling of the papillary body, quite peculiar. It indicates to my thinking a powerful contraction, or at least a want of "give" about the cutis itself, which leads to the stagnation of all the lymph at the margin of the

papillary body, and thus brings about those varicose lymph angiectases.

Bullous Form.

Case D—n. A case of long-standing chronic erythanthema, which first appeared after the use of iodide of potash, and has never wholly disappeared. The earlier, purely pemphigoid character was gradually transformed into an erythemato-papular type which occasionally, especially under the influence of external pressure, passed into a bullous type.

The papules were almost always grouped, arranged in circles or half circles, markedly symmetrical, and disappeared spontaneously in about fourteen days, leaving behind them a bluish, somewhat pigmented, spot. I excised four papules developing into bullæ.

While the four vesicles and blebs of the four pieces of skin showed many differences in relation to their position and the degree of bullous development, the behaviour of the corium in all the preparations is the same, the changes are not limited to the seats of the most marked changes shown by the position of the vesicles, but extend to the whole of the papular elevation. Here also, as in the former case, the lymph spaces of the whole cutis are moderately dilated, and all the blood-vessel walls, especially in the upper half of the cutis, are abnormally rich in connective tissue cells. But while the dilatation of the lymph vessels at the papillary margin is absent, the dropsy of the papillary body is excessive. It looks almost like myxomatous tissue. The papillary body is swollen to two or three times its normal thickness, and consists mainly of a jelly-like transparent, faintly staining substance, in which the connective tissue cells with their wing and feather-like processes are widely separated, and only the vascular capillaries are apparent as strings of cells. The papillæ are swollen to such a degree that most of them have run together to form a level plateau, a few are still separated from each other at their apices. The epithelial ridge-net has for the most part drawn itself out from between them, and the epithelial cutis margin is markedly flattened.

In addition to these changes in the connective tissue, which are evidently only a further development of the slighter changes of the papillary body in the preceding case, there is, further, a new factor, a slight but distinct emigration of leucocytes from the dilated papillary vessels. But this is not a typical character, as is the dropsical transformation of the papillary body, for it is not present on all four preparations. It represents, as in the erythanthemata generally, only an accompaniment of severe cases.

The formation of vesicles begins in almost all cases in the centre of the prickle layer. Certain cells swell up and the compressed cells in their neighbourhood are grouped concentrically around them. Then ensues a blending, later, a liquefaction of the protoplasm, while the nuclei remain longer intact. The cavities, of the size of ten to twenty epithelial cells, contain fluid serous contents with only the suggestion of epithelial remains, or the contents are coagulated, and then usually contain a few leucocytes. Or finally complete liquefaction is absent, and the contents remain a *debris* of softened cell bodies and broken down nuclei, very difficult to analyse.

Like these small, externally invisible vesicles, the larger bullæ are formed almost always in the middle of the prickle layer, but they develope on the basis of a previous severe œdema. The commencement of this œdema is, as in other erythanthemas, an almost universal perinuclear œdema of the individual cells. All the nuclei of the prickle layer at this spot lie free in enlarged nuclear cavities. In some cases the process goes on to a sort of reticular colliquation of the prickle layer, the nuclear cavities continuing to dilate at the expense of the protoplasm, until all that remains of the cells as a resistent scaffolding is the marginal protoplasm and the connecting bridges; and the combination of dilated cells resembles vegetable tissue (Leloir's "Altération Cavitaire"). But there is always, in contrast to the reticular colliquation of infectious processes (smallpox), the difference that the epithelium is only slightly swollen, and that the intracellular cavity-formation proceeds, not from several vacuoles, but from the nuclear cavity alone.

In other places there is a liquefaction of the epithelia, as in many small vesicles, without a scaffolding of cell walls providing any support. The swollen epithelia run together by simple colliquation to a cell cavity, which naturally presents no sharp contour.

In this way there are formed large, flabby bullæ, whose flat base is covered with flattened prickle cells, whose cover contains, in addition to the horny layer, uncornified, flattened prickle cells, and which contain finely granular or thready fibrin and a moderate number of leucocytes. On account of the slow development of the bullæ from the generally swollen prickle layer, there are found only a few compressed trabeculæ, and these indicate, most of them definitely, perhaps all, the compressed ducts of the sweat glands.

Much more rarely and only on limited spots, vesicles are formed in the manner to be described under hydroa, namely, complete elevation of the epidermis from the swollen papillary body. We see from this that the swelling of the papillary body alone is not sufficient to explain this phenomenon, it depends on the relation of the swelling of the papillary body to that of the epidermis. This is, however, in this

bullous erythanthema, not so very much altered, for here the whole epithelium from the commencement shares in the œdematous swelling. Accordingly the base of the most developed bullæ is usually covered with epithelium, and only in rare cases is the papillary body exposed.

Here and there the bullæ, in addition to fibrin and a few leucocytes, contain a mass of fine granules of unequal size which stain with carmine and hæmatoxylin, and have probably arisen from the destruction of the epithelial nuclei in the liquefaction of the cell.

D. ŒDEMA.

Œdema of the skin requires a want of relation between the in and out flow of the blood, and, therefore, conditions relatively unfavourable to the out-flow. Thus it is directly related to the stagnation hyperæmias, and we have already met with it several times (hypostatic hyperæmia in vivo, urticarial erythanthema). Only the *inflammatory œdemas* are an exception to this; and were this definition not used for every kind of swelling which complicates inflammation of the skin, but reserved for the specially severe œdemas which accompany many inflammations, the exception would be only apparent. For in these cases a mechanical stagnation concurs with the inflammation of the skin. The large majority of cutaneous dropsies are the *non-inflammatory* or *mechanical œdemas* which we now consider.

Clinical experience teaches that a simple hyperæmia is never accompanied by œdema, so long as the normal tonicity is not destroyed. Experiment also has fully shown that the obliteration of all the lymph channels of an extremity does not induce œdema. The anatomy of the skin vessels shows a remarkable, and for the simple return of the cutaneous blood quite unnecessary, width of the cutaneous veins. And physiology teaches that during rest, no lymph flows from the incised larger lymph channels of the extremities, although every superficial bloodless incision into the papillary body shows that on the surface of the cutis no inconsiderable quantities of lymph are continually produced.

From these facts we may deduce the evidence, that during rest all or nearly all of the lymph is drawn into the venous circulation, and so returns directly to the heart. The larger lymph vessels, which during rest are almost dry, are, during a simple congestive hyperæmia not affected, for the cutaneous veins are wide enough, even under these circumstances, to transmit both blood and lymph. It follows from these facts, that no hindrances in the way of the lymph channels from the skin to the lymph glands and from here to the subclavia, not even the complete obliteration of the thoracic duct would be sufficient to explain

one single œdema of the skin. We are, therefore, compelled to abandon all these theories of œdema, which seek the cause of œdema in the lymph vessels themselves, either in their closure or when they were open, in a defect of tonicity (Wagner) or of elasticity (Virchow).

The lymph vessels form, physiologically, only a relief track for the lymph during the numerous alterations in calibre of the veins of the skin, brought about by every movement. Greater use of this side track is therefore *ipso facto* pathological and always leads, if of long duration, to a loosening of the skin texture; to œdema. In no case can this abnormal collaboration of the lymph track lie in changes of the track itself; the cause is rather always to be sought in the condition of the vascular track; in a mis-relation of the in and out flow of blood. All changes of the lymph track itself in œdema are secondary in their nature.

We can divide œdema of the skin into *acute* and *chronic*, or *elastic* and *plastic*. When the hindrance to the normal absorption of the lymph by the venous capillaries is suddenly developed, as in urticaria, there ensues a general swelling of the region of the affected vascular cone, which, if sufficiently marked, still further increases the difficulty of the venous outflow, since the increasing pressure within the elastically stretched skin compresses the veins more firmly than the arteries. Thus the filtration of the lymph continually increases up to the limit of elasticity of the skin, and a condition of equilibrium is reached, all the lymph flowing away through the lymph vessels being immediately replaced by an equal quantity of in-flowing lymph. The œdematous region is definitely limited to the distribution of the spastically narrowed vessels. Considerable pressure is necessary to dispel the œdema from this part. The lymph passes very slowly into the tissue surrounding the wheal. It is evidently the still fully retained elasticity of the neighbouring skin which makes more difficult the dilatation of the freely communicating lymph spaces, and tends to the sharp margining of the wheal. After the removal of the pressure the wheal raises itself elastically to its original height or even higher, for the congestive hyperæmia which follows the pressure anæmia at first increases the swelling of the skin. In contrast to the chronic plastic œdema, the acute cannot be massaged away nor does it follow the law of gravity.

The appearances of acute elastic œdema are present most typically in the urticarial forms at their maximum. (See Angioneurosis.) To these and to acute circumscribed œdema (Quincke), are related various forms of spastic œdema which are less well defined; the neuralgic and so-called rheumatic œdemas. In both cases affections of peripheral sensory or motor nerves are concerned, and the œdemas are pretty definitely limited to the distribution of certain nerves, so that a sim-

ultaneous irritation of the vasomotor nerves and a spastic development appear very plausible. This is also favoured by the usually acute commencement and the varying relations of these œdemas. They spread mostly from the cutis itself into the deeper parts, even beyond the panniculus to the muscles, joints, and the periarticular connective tissue, and must therefore certainly be caused by spastic manifestations in the larger vessels.

The *toxic* œdemas can also only be satisfactorily explained by nervous in-coordination in the circulation. In spite of all the trouble that has been taken to find a connection between kidney disease and œdema of the skin, the various explanatory investigations may all be regarded as failures. The hydræmia, and even the hydræmic plethora, of nephritics as such, is, according to Cohnbein's investigations, not sufficient to explain the dropsy in nephritis and scarlet fever. And local disturbances, *e.g.* in the capillaries of the skin, to which we were accustomed to refer in the nephritis of scarlet fever are, according to my investigations, not present, while further, not every local change of the skin, but only narrowing of the veins is sufficient to lead to œdema. We know as yet no anatomical basis for the œdema of nephritis, and such organic changes of the skin vessels would only come into play in the persistent œdema of parenchynatous nephritis. The transient œdemas of contracted kidney, are not compatible with such alterations, but only with a neurogenic origin.

The occasional œdemas in cirrhosis of the kidney are most nearly related to acute œdema and differ from it only in that they preferably appear on the legs, in the region of the ankle, where the skin is thin, deficient in fat and readily moveable ; that is to say, on the predilection area of all œdemas due to general causes.

But if these œdemas are to be considered as spastic, then it is only too easy to consider the persistent dropsy of nephritics as toxic, and of purely functional origin. Here also the anatomical examination of the skin gives, in relation to the vessels, a negative result. The œdema can certainly not be due to a periodically appearing spasm, but only to a persisting increase in tone of the skin vessels. The mis-relation between the in and out flow of blood, which leads to œdema, is distinctly favoured by the dependent position, and appears first, and is most marked on the lower extremities. All the œdemas in the neighbourhood of small primary tubercular areas on the skin and mucous membranes, the puffy appearance of scrofulous children, which many authors recognise, as a condition distinct from tuberculosis and favouring the development of that disease, under the name Lymphatic Constitution (or " Lymphatismus "), are to be explained in the same way. Usually it is the skin of the eyelids, the nose and the upper lip,

the lower part of the cheek and upper lateral parts of the neck above the maxillary glands, which show this primary tuberculous œdema. This localisation corresponds exactly with the first appearance of tuberculosis on the conjunctiva and cornea, the nasal mucous membrane and the meatus auditorius.

With these toxic œdemas we enter the domain of the chronic œdemas, which are accompanied by persistent loss of the elasticity of the skin. The dropsy on the legs of nephritics presents, after long duration, appearances which differ in every particular from that of the elastic œdema described above. The dry, distended, bluish white, shimmering skin may be easily pitted and kneaded, it has become plastic, no elastic resistance is perceptible on pressure. The fluid which has been pressed to one side returns very slowly, a depression remains for a long time ; the elastic tension of the skin, which varies from point to point, has disappeared from over-distension, and in its place we have an equal hydraulic pressure. During rest the fluid sinks, inside the skin, to the lowest point, but is everywhere easily retained by external pressure, bandages, or tight-fitting clothes. External pressure may even, if long continued, restore to the skin a certain amount of its elasticity.

With the chronic, spastic, purely functional œdemas I would place also the *cachectic* and the *paralytic ;* in both forms the histological observations are, so far as concerns the vessel structure, absolutely negative. The œdema in paralysis of the extremities is explained by an incongruity in tone of the hypertoned vessels, which are no longer under the influence of the central, but only of the peripheral ganglia. From the paralysis there ensues, first an anæmia, and from relative weakness of the arterial tone—œdema. The action of gravity naturally leads in paralysed limbs to œdema, and therefore paralytic œdema is mostly found in the ankles, legs, and backs of the hands. Less clear are the relations in cachectic œdema, for it is difficult to limit the definition. When in wasting diseases, without the intercurrence of heart or renal affection, œdema finally appears on dependent parts of the body, it certainly does not depend on the poor condition of the blood in general; on hydræmia. For we have at the same time an anæmia, and therefore an accommodative diminution of the whole cutaneous circulation. But we know that all hypertones tend to œdema ; that an in-coordination between the arterial and venous tones readily developes. It appears to me that we can most readily find the explanation for such predominance of the venous tone in the so-called cachectic œdema, in the absorption of toxic products from the tissues. In particular we certainly know that under the persistent influence of phthisis the skin gradually acquires peculiar qualities. As the first and most

superficial, so-called scrofulous affections give rise to œdema, the later clubbing of the finger ends indicates a specific stagnatory action of the poison. In the final stage, where the cachectic œdema and the colliquative sweats appear, the skin becomes a good medium for the bacilli; there occur true tubercular ulcers and caseous degeneration, which are not usual in the skin (see Tuberculosis of the skin).

The previously considered functional œdemas form only a small part of all mechanical dropsies. Much more frequent and comprehensible are those dependent on external or internal mechanical misrelations, not functional, such as are induced by external pressure, gravity, local thrombosis, and general venous stagnation.

The forces which have to be considered in mechanical œdema are better understood by recalling the equation, which holds as well for the physiological separation of lymph as for all œdemas (inflammatory and not inflammatory);

$$l = a - v$$

in which a. indicates the amount of fluid passing along the section of a cutaneous artery in a unit of time, v. and l. the amount of fluid which in the same time flows through the corresponding veins and lymph vessels. We ignore the insensible loss of water and the small amount of fluid which remains in the skin for the purpose of growth and nourishment.

In this equation lies the explanation of *compression œdema*, in which every narrowing of the venous segment results in a diminution of v. and a corresponding increase of l. But it is to be noted, that the amount of œdema depends, less on the high degree of obstruction in certain venous trunks, than on the circumstance whether all or at least most of the veins of the region have suffered a diminution in their lumina. In the latter case the resistance may be slight and yet have as its result a more marked œdema than the complete obliteration of the cutaneous veins. We have to do with the same factor as in stagnation hyperæmia, viz., the collateral circulation. Therefore circular compression of the extremity (with a bandage, a garter) is one of the surest means of invariably inducing an œdema even on healthy skin; not because the lymph vessels are compressed by it, for that alone would not cause a trace of dropsy of the skin, but because the veins of that whole part of the body, are more firmly compressed than the more rigid arteries and thus v. is in comparison with a. more quickly diminished. An elastic bandage so powerful that both arteries and veins are rendered equally impervious does not, as is well known, cause œdema of the limb.

Gravity is the second main cause of dropsy in the narrower sense. As we have already stated in connection with stagnation hyperæmia, this action is not to be understood as if the pressure

of the blood column was simply added on the legs to the internal pressure, which is present in the veins, and was therefore altogether an overpressure. In that case a similar overpressure with a tendency to œdema would be constantly present in healthy persons. There it is compensated by the natural aid of a stronger tone of the vessels, both of the arteries and the veins. Now we saw that this venous stagnation with its results of passive distension and formation of varices developed on the basis of this increased vessel tone as a "hypostatic hyperæmia in vivo" if the increased tone of all the vessels almost arrested the vis a tergo. A necessity of every stagnation œdema due to gravity is however, as in every œdema, an increase of the difference a. –v. Since the arteries of the leg on their side oppose the constant pressure of gravity on them by increased tone, so a. can possess no abnormally high value, and there is no reason why, without any other change, v. should not exceed a. Therefore we do not find the same amount of œdema in all varicose legs, indeed it is only present in a minority of cases. The necessary addition is, either an increase of a. or a diminution of v.

A yielding of the arterial tone is found in the gravitation œdema of young growing persons, such as bakers and waiters, who pass much of their time on their legs, just as in these individuals, through insufficiency of the muscles and ligaments, flat-foot developes. In older people we see occasionally from artificial irritation or eczema, a hyperæmia of the varicose leg, and with it an increase of a. and the occurence of œdema; but this belongs to the category of inflammatory œdema. Non-inflammatory œdema from diminution of the arterial tone is present only rarely in later life, and then only in old and weakly individuals.

It is the œdema from diminution of v. which affects those of riper years. The increased difficulty of the venous outflow from ever-increasing hypostative hyperæmia has here especially to be considered. Here and there the barriers which the valves oppose to the formation of varices are gradually overcome by the action of gravity, the hypostatic hyperæmia reaches the small valveless veins, weakening their tone, and annulling their power for absorbing lymph. The skin of these places on the leg and on the ankle becomes puffed up and coloured blue or violet from the widely-dilated subcutaneous veins shining through. There forms a red net of cutaneous veins, a capillary hyperæmia, and finally there is diapedesis of red blood corpuscles, necrosis and the formation of an ulcer on the affected spot.

General venous stagnation acts on the skin of the whole body, like gravity on the dependent parts. In uncompensated failure of the heart, along with the increased difficulty of entrance of blood into the

right heart, œdema appears first on certain predilection areas; with the facilitation of the venous outflow, it again disappears, but ultimately developes into general dropsy. The œdemas of heart disease are thus purely mechanical.

First in the fourth line, *venous thrombosis* must be mentioned as a cause of œdema. It is only rarely that the veins of a region with all their collaterals are plugged, as by plaster thrombi in the investigations of Solnitschefsky. That would certainly lead to the highest degree of œdema, stasis, and gangrene. Thrombosis of the crural vein induces, in otherwise healthy people, merely an œdema of the ankle and back of the foot, and this disappears in a few days under appropriate elevation and mechanical compresses, if the venous collaterals sufficiently dilate. To the mechanical œdemas are to be added, fifthly, certain cases of so-called *collateral œdema.* Under this name are grouped diffuse swellings of the skin and subcutaneous tissue, which appear over deep collections of pus, in the subfascial, intermuscular and periosteal connective tissues, over pleural exudations, on the skin of the face, in abscesses of the gums and of the Antrum of Highmore, on the prepuce, in the presence of shankers, and on the eyelids in every inflammatory affection of the neighbourhood. They increase with the softening and the enlargement of the inflammatory area, are neither hot, red, nor painful, and, after surgical relief of the tension in the deep area, immediately disappear. These radiating œdemas are not all of the same origin. Only very few of them can be considered as truly inflammatory—that is, as a low form of inflammation (Cohnheim, Rindfleisch, Birch-Hirschfeld, Ziegler). For most of them the older view is more correct, that they consist of a serous exudation, developing in the inflammatory area and driven into the neighbourhood by the increasing pressure (Hüter, Roser, Zimmermann). And in those œdemas which appear still further away, in overlying tissues (skin of the chest in empyema of the pleura) we have to dispense with the inflammatory and pressure theories and fall back on simple stagnation (Bardeleben, Billroth, Hüter, Recklinghausen). This may develope from compression of the veins inside, or at the side of the inflammatory area, but also far away wherever some other and the œdematous region empty their blood into the same large veins. To Klemensiewicz we owe the proof that the veins coming from inflammatory tissue are dilated. Thus a collateral backward stagnation of the blood in the neighbourhood of the inflammatory area may easily develope. The stagnation œdemas, like the pressure œdemas, are then, through the collaterals, mechanical in their nature; the latter will present greater quantities of albumen and leucocytes (where the primary area is purulent) than the former.

We can in all these mechanically-induced œdemas, as in the toxic, distinguish *acute elastic* from *chronic plastic* forms. The œdemas due to compression, venous thrombosis and collateral stagnation provide more examples of the former, the dropsies due to the gravity and general venous stagnation, more of the latter. But of course prolonged compression—*e.g.*, beneath a circular scar of the leg—may lead to a plastic œdema of the ankle. Both forms are distinguished as mechanical by a common character, from the inflammatory œdemas to be afterwards described; they contain a tissue juice of the same salinity as blood serum, with considerably less albumen, with fewer leucocytes and relatively more red corpuscles. The amount of albumen diminishes in long-standing œdema.

But there are great differences in their action on the cutaneous tissue. The acute, elastic œdema shows no other changes than are caused by the mechanical dilatation of the lymph spaces. According to the seat of the œdema, in one class of cases, the lymph spaces of the whole cutis, the papillary body and the hypoderm are equally dilated, in another class, on the contrary, especially the large lymph spaces of the subcutaneous tissue and the lymphatic sheaths of the larger vessels at their entry into the cutis. The best view of this lacunar system is obtained on moderately thick sections which are stained for elastin. While usually the net of elastic fibres runs regularly through the collagenous bundles, it is, in acute œdema, displaced by the stretching of the collagenous bundles still more markedly than they are. Sometimes diverging rows of elastic fibres are pressed together into thick bundles, sometimes, where they are stretched over wide spaces in the tissue, they are strained or even torn. In addition to the lymph spaces, the lymph vessels are also dilated, but not in such a degree as the lymph spaces, and not by a long way so markedly as in long standing œdema. The blood vessels of the skin and the papillary body show no dilatation and are empty, which is not surprising, since the skin in acute œdema presents an unusually high internal pressure. On the contrary the subcutaneous vessels, and especially the veins, are wide. The greater contraction of the vessels can only be observed if the spastic œdematous skin is removed during life and immediately fixed in osmic acid or tannin. The collagenous tissue shows no change except mechanical separation. The epidermis is everywhere normal and so are the follicles, coil glands and muscles, except that in more marked œdema, they are surrounded by large lymph spaces. Of a local leucocytosis or other signs of inflammation, as described by some authors, there is, in the purely spastic, acute, uninflammatory œdema, no trace.

The longer the œdema exists the more the skin suffers. First the

type of the spaces is altered. In place of the large scattered holes, which immediately strike one in acute œdema, we find a number of smaller and medium-sized ones, equally distributed through the whole cutis, which thus appears widened, sodden and porous. The thicker collagenous bundles are thinned out by the pressure of the lymph spaces, their rigid arrangement is more or less gone and their course has become more wavy. The elastic tissue disappears the more the longer the œdema lasts. We notice first the effect on the elastin of the papillary body. The fine tendrils are thinned and finally completely disappear, from the epithelium downwards. In old cases of œdema of the leg, in nephritis, heart disease, etc., the elastic net of the papillary body is completely lost, while the collagenous, formerly finely fibrillated tissue appears flabby and wide-meshed, like mucoid tissue in its texture, but without any mucoid or spider cells. The papillæ are swollen, rounded and flattened, and the epithelium consequently also rounded and flattened. The elastic fibres of the cutis also are for the most part gone, those which remain are thinned and stain feebly, they are often stretched in the direction of the chief swelling of the cutis. They often end in fine points, such as one normally sees only in the papillary body. On the most elastic parts of the skin, as for example the scrotum, the disappearance of elastin is relatively greatest.

Owing to the loss of elastin, the œdematous skin gradually loses more and more elasticity, that is, the spontaneous elastic recoil of the collagenous tissue, displaced by pressure or by movements of the body, takes place more and more slowly and incompletely, the muscles of the skin lose a great part of their action on the skin texture. Thus we have an additional factor, favouring the œdematous swelling of the cutis. By the œdema directly attacking the elastin, it interferes with the most important factor in the healing of œdema, and induces an incurable " Circulus vitiosus " which terminates in complete loss of resistance of the skin, rupture of the epidermis and Lymphorrhœa externa. Possibly in time the muscles also suffer, but they had not done so in the specimens I examined.

If the œdema persist, the subcutaneous fatty tissue also undergoes retrogressive changes. The fat drops diminish, until finally simple endothelial plates, separated by large, irregular, collapsed lymph spaces, occupy their place. The whole fatty lobule shrinks to a half or a quarter of its former size and resembles a collapsed, coarse, spongy tissue, in which very much narrowed blood vessels, and here and there atrophic or œdematous coil glands are embedded.

The epithelial appendages of the skin are long unaffected by œdema, they undergo either retrogressive metamorphosis, like the surface

epithelium and the hair follicles, or they swell up and participate in the œdema, like the coil glands. Finally by ever increased bad nourishment (want of oxygen) the epithelium atrophies and no longer proliferates; the surface epithelium diminishes, chiefly in the prickle layer, while the horny layer retains its thickness for a long time, with diminution of its fat. Finally the surface epithelium is so stretched by the increasing tension of the œdema of the swelling papillary body, that it ruptures. The formation of hairs ceases, and after their loss the hair follicles shrink to mere rows of cells.

Gravitation œdema and it alone differs from the ordinary mechanical œdemas, for here a hypostatic hyperæmia not only accompanies but induces the whole process. In this case in the swollen bluish red skin of the leg, even in the corpse, the blood vessels, especially the veins and capillaries, are fully dilated, in some so markedly that the appearance of angioma is suggested. The vessel walls in the cutis and the papillary body are thickened by a new formation of cells. The whole skin is abnormally cellular, which is not the case in simple œdema, and there are found, irregularly distributed, large spindle cells rich in spongio plasma and with a fair amount of granular protoplasm. Around the vessels, particularly at their bifurcations, pretty large plasma cells are found. Where these are more congregated, the skin has, in places, the appearance of granulation tissue, to which appearance the width of the vessels and the interstitial œdema contributes. Apart from these progressive changes, we find all the other symptoms of mechanical, chronic œdema, splitting of the collagenous, disappearance of the elastic tissue and atrophy of the epithelial structures. Sometimes we have on the contrary a hypertrophy of the ridge net, in other cases, where the venous stagnation has reached a higher degree, the epithelium is loosed from the cutis and a bulla is in course of formation. A more or less distinct accumulation of pigment, particularly in the upper part of the cutis and in the papillary tissue, frequently derived, in the last case, from limited, probably diapedetic, escapes of blood, completes the picture of this stagnation œdema. From this to the elephantiasic thickening and warty hypertrophy of the surface, such as we meet in Elephantisis nostras and in Ulcus Cruris, there are many stages; the interstitial œdema inside the connective tissue bundle in these cases disappears, they become thicker, and their spaces filled with cells rich in protoplasm, while the larger space and the lymph vessels show a marked dilatation; with this collagenous hypertrophy is usually combined a new growth of epithelium, less in the appendages than on the surface.

Here follows a long discussion of Heidenhain's views, which Dr Unna thinks it unnecessary to reproduce in this English edition. N. W.

We enter on quite a new region in considering *inflammatory œdema.* We must, in order to have before us a uniform class of examples, exclude a whole series of œdemas, which up to now have mostly been ascribed to an inflammatory cause. These are the toxic, urticarial, neuralgic, rheumatic, nephritic, and most of the collateral œdemas, which we have already, partly on theoretical grounds, partly from their almost negative histological character, ascribed to a mechanical cause. The definition of an inflammatory œdema is only justified where a true inflammation—acute, subacute, or chronic—is present. So this chapter can only be properly treated as an appendix to the inflammations, and it is indeed neither advisable nor necessary to describe in this place all of those dermatoses in which an inflammatory œdema is found. It is sufficient here to note the genesis of this appearance and the fundamental difference, which in the widest sense of the word exists between it and the mechanical or stagnatory œdemas.

As we shall see in the chapter on inflammation, we regard as the centre point and primary symptom of every inflammation, a fluid exudation. It is not necessary that this shall be in all cases recognisable as such, macroscopically and microscopically. It may be fully spent in parenchymatous œdema, in a swelling of the cells and intercellular substance, or even lead only to stoppage of the growth and appearances of proliferation. When in such cases other appearances of inflammation are present we have sufficient ground to regard the affections as inflammatory and so make up our clinical deficiencies. But we can naturally only expect an inflammatory œdema in those inflammations which produce a large amount of exudation, which does not disappear in the parenchyma, especially in the sero-fibrinous and purulent inflammations of the skin.

While in the mechanical œdema a *transudation* is produced, *i.e.*, a 2%-3% lymph relatively poor in albumen and formed ingredients; in the inflammatory œdema an *exudation* leaves the blood vessels, a lymph rich in albumen and blood cells, approaching the composition of blood serum. The transudate is produced through a mechanical misrelation between the in and out flow of blood; it is pressed into the tissues; at least, this mechanical theory of their development suffices for all known transudations. The exudation in inflammatory œdema, as in every inflammation, is under the influence of a chemical traction power, induced in the tissues by the irritant which produces the inflammation; it is drawn from the blood vessels. The transudates in the different mechanical œdemas are very similar in their composition, and differ, as well as quantitatively, chiefly only through the rapidity or slowness of their development and the varying duration of their existence;

all these circumstances have of course a reaction on the composition of the transudate in virtue of the greater or less watering of the tissue caused by it. The exudations vary very much, for the chemotactic power which draws them from the blood at the same time makes a selection among all the formed and unformed constituents of the blood; in short, no two exudations are alike. Nevertheless we can distinguish great groups of exudations-—the serous, sero-fibrinous, leucocytic, fibrino-leucocytic, hæmorrhagic, &c. The serous and fibrinous inflammations of the skin furnish the majority of the inflammatory œdemas.

When we recollect that the stream of exudation flows in a diametrically opposite direction to the normal course of the cutaneous lymph into the venous radicals of the skin—-the leucocytic exudation is demonstratively drawn partly from the venous radicals—we see that every inflammation produces conditions of the lymph stream which interfere with the power of absorption of the cutaneous veins. Therefore every severe exudative inflammation of the skin is combined *eo ipso* with a *swelling of the tissues*, a tumour. Were the four cardinal symptoms of inflammation not taken from the skin, but from the lung or the stomach, the "tumor" would certainly not have had such a prominent place (the Functio laesa would have been more prominent).

But we must not yet regard as inflammatory œdema the swelling which is to be found in every severe serous and fibrinous inflammation. For example, every eczema is accompanied by marked fibrinous exudation, and every erysipelas, be it ever so slight, with a marked swelling, now of the papillary body now of the whole skin. But we speak of the œdema only when the skin is swollen to twice or thrice its normal depth, is shiny, stretched, and in long duration of the condition, doughy and easily pitted; this condition complicates eczema, especially of the face, where, in addition to the parasitic catarrh, we have a dermatitis induced by chemical or physical irritants, a severe effect of the weather, an unsuitable medicine or the like, or when erysipelas has led to widespread venous thrombosis.

In the former case the inflammatory œdema developes through a complication of the already existing inflammation of the skin with spastic, in the latter case, with ordinary stagnatory œdema. Idiosyncrasies to certain drugs form a large contingent in the one, tight bandages, the action of gravity (in eczema of the legs) in the other, form of complication. The fibrinous inflammations of the skin have a natural tendency to the production of inflammatory œdema, in that they favour the development of thrombosis of the blood vessels, as do erysipelas, progressive phlegmon and elephantiasis nostras.

According to this etiology it is very evident that we cannot supply a uniform picture of the inflammatory, as of the mechanical œdemas.

The primary inflammations indicated, supply the basis on which every one developes, and the anatomical appearances change therefore from case to case. We can only give a few general points corresponding to those of mechanical œdema. When it begins acutely, one is able to recognise, in addition to the symptoms of the primary inflammation (for example, eczema), widely-dilated lymph spaces, and a pushing aside of the elastic net, as, for example, in urticaria. Longer-standing œdemas lead to the disappearance of the elastic tissue, to the general breaking up of the fibres of the collagenous tissue and to disappearance of the fat, if these changes have not been already brought about by the primary inflammation (as in erysipelas). But further, œdema on the base of inflammation has a secondary action in many of the changes. Vesicles become large bullæ, slight elevations of the epithelium lead to widespread separation of the cutis, degenerated and usually dry parts of the epithelium and connective tissue become converted into moist, swollen, homogeneous, glassy, hyaline substances.

E. HÆMORRHAGE.

The hæmorrhages of the skin are distinguished clinically as such from hyperæmia on one hand, and angioma on the other, by this fact, that their red colour does not disappear under the pressure of the diascope, but at most—through emptying of the blood vessels—becomes a shade lighter. Nevertheless the escaped blood, free in the tissue, is not immovably fixed there; a prolonged pressure can dislocate to a limited extent the elastic and usually uncoagulated mass of blood corpuscles; especially is this the case in the subcutaneous hæmorrhages, less in the cutaneous, and least of all in the epidermic and sub-epidermic, which, on account of their intense red colour, can only be distinguished from small superficial angiomata by their immovability. The red colour if deeper lying appears blue; if the hæmorrhage reaches from the papillary body to the hypoderm, a deep blue colour mingles with the red of the surface, and if it begins first in the deeper layers of the cutis and reaches through the whole sub-cutaneous tissue, it then appears on the surface steely-blue to blue-black, even although the cut surface is pure blood red.

The form of the hæmorrhages is, in the deep-lying and deep-reaching ones, round and deformed, in the cutaneous and epidermic, irregular, often jagged and star-shaped, but more sharply contoured. According to the size of the extravasation the skin-surface may be unaffected or more or less elevated in the form of a boil; but here also the epidermic hæmorrhages are distinguished, for the smallest of them cause nodular projections of the surface. Further, there comes into consideration the

consistence of the sub-cutaneous tissue and of the underlying parts, as well as the tension and fixation of the skin. Large escapes of blood of the same size, form, on the fatty skin of the abdomen or of the buttock only diffuse swellings, on the skull a thick, firm tumour, and on the thin skin of the aged a flabby, sack-like, pendant, doughy tumour.

We divide hæmorrhages according to their size into *Petechiæ* (the size of mustard seeds to peas), *Ecchymoses* (peas to half-crowns), and still larger flat ones, *Suffusions.* The deep-reaching and extensive ones which elevate the skin we call *blood boils, Hæmatoma, Ecchymoma.* Peculiar breaking up of the skin analogous to the tissue changes in hæmorrhagic infarctions of other organs are very rarely seen; the name is most applicable to those blood boils caused by protracted escape of blood, such as develope in child-birth on the vulva, or after prolonged cupping. In general the skin is on the one side too firm, on the other too elastic for this; it yields slowly to the overpowering pressure of the out-poured blood; its structure is loosened but not entirely destroyed.

That the blood vessels of the skin are by no means disposed to hæmorrhage, we learn, on the one hand, from the numerous Sectios, in which many internal organs show hæmorrhage, while the skin is entirely free, and from the equally numerous experiments on animals, in which general ecchymoses of the internal organs, but not of the skin, is produced by the injection of toxic substances into the circulation, and on the other hand from the close examination of those injuries which especially induce hæmorrhages on the skin. We exclude here the hæmorrhage caused by incisions, and by the sting or bite of animals; from these injuries it is evident that only the blood vessels of the bones are protected. But simple blind force, even when it is severe, by no means invariably produces bleeding on the skin. A severe blow on a part of the skin which is not especially rich in vessels, and through muscular tension or movement of the limbs is momentarily anæmic, as the skin on the extensor surface of the extremities, or over bony processes and joints, leads rather to total anæmic necrosis than to bleeding. Unexpected blows are more liable to cause bleeding than those in which the blow, through voluntary tension of the skin, is to a certain extent parried. The surest method, on the other hand, of inducing bleeding is *pinching* and *nipping* of the skin, that is, the exercising of a pressure in which, through pulling or folding, a limited amount of blood is retained in the compressed portion of the skin. The incompressible blood fluid in this case bursts the vessel coats, and under certain circumstances even the whole skin. Bumps and blows which are capable of pressing the blood out of the skin hardly ever cause bleeding; but otherwise the same injuries can readily induce slight

ecchymoses on a skin already hyperæmic from another cause, as, for example, on varicose legs and on chapped hands and ears.

Negative pressure through *sucking* with the lips, or by the cupping glass, acts in the opposite way to positive. The strength of the pressure is in these cases much less, and yet there immediately ensues a not inconsiderable bleeding, simply because the distended vessels are all over-filled with blood; a prolonged negative pressure can convert the whole skin as well as the hypoderm into a spongy tissue soaked with blood, and finally burst the tissues of the skin.

Aspiration and *squeezing* are the surest means of tearing the healthy blood-vessels of the skin. It is the high tone of the skin-vessels and the easy, thorough emptying of the skin of blood, which prevent the development of cutaneous bleedings. We must bear this in mind in judging of the much more puzzling cases of non-traumatic bleeding. For it is very remarkable that while even gross traumata only under particularly favourable circumstances can induce bleeding in the skin, there exists a whole class of dermatoses, the purpuric diseases, in which not even the smallest traumata are necessary to produce wide-spread ecchymoses, and in which a series of diseases shows the bleedings only in the skin and not in other organs (Purpura simplex, Purpura hæmorrhagica acuta, Peliosis rheumatica). This paradoxical contradiction points out that especially for the skin-vessels, which are so slightly vulnerable, quite peculiar causes and conditions must exist, *specific causes of the bleeding*, which have recently been much sought for without success.

It was then quite natural that in the skin, with its purpuric diseases, one formed pretty generally such ideas of the mechanism of bleeding as made unnecessary gross lesions of the well-protected skin-vessels; *i.e.*, one readily grasped the theory of diapedesis, first described by Stricker and then by Cohnheim. The less easily skin-vessels rupture from many gross wounds, the more *à priori* probability is there of the existence of an infiltration of blood, a diapedesis of the skin-vessels in general, and in the purpuric diseases in particular. I had myself, even before I had personal experience of the histology of the condition, sharply separated the two processes of rupture and diapedesis, and hoped to obtain from the examination of cutaneous hæmorrhages a confirmation and better knowledge of diapedesis.

But the careful work of Dr Sack, undertaken under my direction, whose results I can personally confirm and amplify, leads in direct opposition to this *à priori* view incontrovertibly to the conviction that in almost all cases of cutaneous bleeding, both in purpuric diseases and in the intercurrent bleedings of other chronic and acute febrile processes, rupture of the vessels is really present. Further, it shows

that a distinct diapedesis is only present in a few special cases. As a whole we have to regard the non-traumatic hæmorrhages of the skin also as the results of rupture, and especially to study the manner of its origin. The less easily the ordinary injuries of the skin cause a rupture of the vessels, the more necessary is it to distinguish the more remote from the immediate conditions of bleeding, the preparatory tissue changes from the mechanism of the actual rupture. Just on account of the difficulty of explaining cutaneous bleeding, observers have always occupied themselves in noting all visible changes of the vessel walls, and were only too ready when they found them to bring them, whatever the circumstances, into connection with rupture. And yet it is quite apparent that one can only clear up the point, whether a vessel or tissue change has really favoured and induced the bleeding, by a more thorough investigation into the act of rupture itself. Before we concern ourselves with the preparatory tissue changes, we must more thoroughly understand the *mechanism of vessel rupture* in the skin.

Unfortunately in most cases we can only get a limited number of preparations of definitely torn blood-vessels, and it is scarcely possible from these few sections to demonstrate the whole of the mechanism of bleeding. Here I succeeded first on a definite object, which I would specially recommend to other investigators—namely, on those pieces of skin in which during life a (*e.g.*, infectious) cause of skin bleeding was present, but after death, *through the development of hypostatic hyperæmia*, the blood suffusion persisted. Then one finds in every section of this spongy, blood-soaked tissue evidences of rupture and the blood-vessels in every stage of bursting. Although on such preparations there is little to be learned as to the remote causes of bleeding, they are particularly well suited to explain the mechanism of rupture.

One finds here in the middle of all the larger masses of blood, both in the hypoderm and in the cutis, a number of connective tissue streaks, which may be recognised as sections of plates, and although lying free in the escaped blood, allow one to recognise a frequent arrangement in ring or tube form. One may trace them here and there up to definite segments of tube-formed organs—namely, enormously dilated blood-vessels, whose yielding walls are reduced to single plates. At first these are partly adherent, arranging themselves like tiles, or concentrically round the larger vessels like the flakes of a fir cone. Further, there are present straight or bent interrupted lines which can finally be, with some difficulty, recognised as fragments of the vessel walls. It is questionable whether not only the vessel walls but also the fibrous bundles of the cutis are loosened, torn and separated from

each other by the bleeding. In the largest hæmorrhages we always see both isolated connective tissue fibres and endothelial plates. In the differential diagnosis one has chiefly to note that the latter can be followed on the same or subsequent sections into still unruptured vessels, and that, on the contrary, they do not pass into twisted threads and fibrous bundles, that they are stiffer and smoother and usually bent to a common centre, in contrast to the much twisted, isolated connective tissue fibres, and that finally they usually occupy the centre of the largest lakelets of blood. On the contrary, the recognition of endothelial cells and nuclei in contrast to ordinary connective tissue cells of the cutis is made only with difficulty, or not at all; for the latter also, are, inside the hæmorrhage, flattened out to their maximum, and powerful nuclear stains are necessary to bring the flat atrophic nuclei to view. Where on such a collagenous fibre in the centre of the hæmorrhage several nuclei, on the same side and in regular relation, follow each other, that is a sure indication of a fragment of the vessel wall; but this is only rarely seen. But when one has studied the appearances of rupture on such pieces of skin, he will, in most cases, soon decide whether he has to do with ordinary split-up connective tissue or with ruptured vessels.

When, with this experience, we approach the ordinary cutaneous bleedings of less extent, especially the purpura forms, it is evident that, in the preponderating number of cases the bleeding is limited to the upper part of the hypoderm and the lower part of the cutis, that is, to the region of the deep vascular network; rarely it extends to the level of the papillary body, and still more rarely is it found here alone, and in the epithelium (traumatic bleeding). These circumstances suggest that on the under surface of the cutis there must lie a "locus minoris resistentiæ" in the otherwise so well protected skin vessels. It is not the yielding of the subcutaneous tissue, as such, which is here concerned. For then the bleeding would be found where the panniculus is thick, chiefly in the under half, and not, as is the case, chiefly in the upper. And such an explanation would further not be comprehensible, since, in the subcutaneous tissue, both arteries and veins possess a strong adventitia and a relatively stronger media. As the vessels inside the cutis, in spite of their delicate, almost capillary walls, are protected by the rigid tissue of the cutis itself, so are they in the hypoderm by particularly strong walls, rich in elastic and muscular elements. It occurs at once that the above-suggested seat of diminished resistance may be seated exactly at the boundary of both protective apparati, where the strength in the vessel walls suddenly markedly diminishes and they enter into the relatively rigid cutis, deprived of their own protective apparatus. Every circumstance which interferes with the

exact approximation of the two protective apparati must provide an opportunity for bleeding. For example, a simple maximal filling of all the vessels of the cutis with blood, if the cutis cannot correspondingly stretch itself (as for example in pinching), must lead to the unprotected vessels of the cutis being drawn a short distance into the unresisting hypoderm, forming a small but complete interruption in the protective apparatus.

The more certain appearances of rupture in ordinary non-traumatic bleeding, in Sack's and my own preparations, do not exactly contradict this view, in so far as they are always associated with thin walled veins at the margin of the cutis and sub-cutis. Either the tear goes through the whole wall or only through the endothelial coat, which appears raised up and rolled together, and probably or evidently corresponds to a tear of the outer coat at another part of the vessel, through which the blood pours into the tissue spaces of the cutis. But these torn vessels always have the type of sub-cutaneous vessels with well formed media and adventitia, and their destruction, if we regard it as the primary occurrence, has always for us something incomprehensible, for the constituents of the wall are otherwise perfectly healthy. It is also clear that the appearances by no means correspond to what I have described above of rupture, which is easily understood, and capable of only one meaning. Further, they are certainly not constantly recognisable in every case, and therefore have been rarely seen by earlier observers.

This last dilemma in the rupture question has its explanation, I believe, in the fact that most of the ruptured vessels of sub-cutaneous type were found on vertical sections of skin. If one reflects that the sub-cutaneous vessels, before they enter into the cutis, have a longer or shorter, almost horizontal course on the cutis and sub-cutis margin of most regions of the skin, vertical sections will give almost always transverse, and only rarely, accidentally, longitudinal sections of these vessels. Now while it is for thick walled-vessels of sub-cutaneous type pretty much all one, in this investigation, how they are met, for the tear is always evident, the case of the transition forms, of cutaneous character, is otherwise. A vessel of that class, longitudinally met and capable of being followed, will seldom be recognised, cross cut ones, almost always: it must be, then, that we have accustomed ourselves, as I have described above, to recognise the membra disjecta of such a cross section inside the mass of blood.

In this connection it is a methodical advance, if we examine the cutaneous hæmorrhages chiefly on horizontal sections and thus meet longitudinally and can follow the transitional vessels, from which the hæmorrhages chiefly come. Since I adopted this plan, I have been able

in every case to discover the seat of rupture, and the appearances correspond much more with those described at the beginning, in that the splitting of the weakened walled vessels takes place in entirely analogous fashion.

Here, at the part of the vessel, no longer protected by its thick walls, and not yet by the tissue of the cutis, I find the "locus minoris resistentiæ" and the primary seat of the rupture. The numerous but not constant, among themselves morphologically different, tears of the deeper lying stretches of subcutaneous type I regard as secondary, induced by the chief rupture. This explains not only their inconstant changeable character but especially their existence at all, which, without this conveyance from less resistant parts, appeared to me inexplicable.

Without wishing to conclude that all bleedings of the deeper layers of the skin must take place in the thinner walled vessels of the hypoderm at their entry into the cutis, and willingly admitting that peculiar anatomical conditions and special external circumstances may have the effect of prolonging the rupture further outwards or inwards, I should wish to consider a rupture of the vessels at this seat of lessened resistance as the normal cause of far the greater number of cutaneous hæmorrhages. This view has on the one side a sound anatomical basis, and on the other in its favour all the histological facts at my command.

If it has then become possible to understand the *mechanism of rupture* of the skin vessels, in the narrower sense, better than before, we are from this positive basis now in a position to decide what *rôle* the different *preliminary changes*, which up to now have been recognised partly as real sufficient causes and partly as favouring factors, play in hæmorrhage.

At first, *changes in the vessels* were considered as the cause of rupture and they have most diligently been sought for. Babes has, in infectious purpuric diseases, recently seen, in certain cases, molecular destruction and defective formation of the vessel walls—and has here been evidently more fortunate than most other observers—in other cases a specific hyalin degeneration of the same. So far as concerns the first suggestion, detailed information is still to be awaited, and it is indeed not only probable, but a notorious fact, that bacteria, and other parasites circulating in the blood, exercise under certain circumstances a marked toxic effect on the cutaneous vessels. But this by itself is not sufficient to explain one single hæmorrhage of the skin. One has only to think of the tremendous paresis of the vessels and congestion of the skin in scarlet fever, which usually runs its course without any bleeding, or on the embolisation of the skin with

strepto-cocci (see Phlyctænosis streptogenes) and staphylo-cocci (see pustolosis staphylogenes) in which large areas of adjacent epithelium even become necrotic, without bleeding appearing simultaneously in the skin. Why, we see even a primary necrosis of the embolised capillaries of the skin develope, for example in glanders, without hæmorrhage as an addition, simply because the necrotic vessels are for long stretches filled with infectious thrombi. On the other hand we are compelled, on clinical grounds, to admit in certain purpuric diseases (Purpura hæmorrhagica chronica, Scorbutus) of a disposition depending on an infectious basis, which becomes manifest on slight Traumata (Purpura factitia). But whether this consists in a molecular fragility of the blood vessels or in other conditions is still absolutely unknown.

The question of the infectious vessel degeneration is in this position; that its existence in many cases in the skin is proved, that a *neccssary* connection of it to skin bleeding *ccrtainly* does *not* exist, but that in certain cases a preparatory influence of the infection is very probable. But it must be proved in each case and its mechanical action investigated.

Less favourable is the question in relation to the *hyalin degeneration* of the vessels. This is present often enough in lichenous and sclerodermatic diseases of the skin without ever being accompanied by a bleeding. I found indeed in a sarcoma of the skin a widespread hyalin degeneration of the vessels without the concurrence in this sarcoma of the usually so frequent bleedings. That the hyalin degeneration of single skin vessels can by itself have hæmorrhages as its result, no one can seriously hold; its result can only be partial anæmia of the skin. But widespread degeneration of the capillaries which has not been recognised can hardly have an influence favouring bleeding. For the hyalin degenerated vessels are thickened in their walls, and are certainly not more fragile than normal, while a collateral hyperæmia so great as to induce bleeding is likewise unknown, at least on the skin. Equally problematic is the assumption of *amyloid* disease of the capillaries as the origin of the cutaneous hæmorrhages of syphilitics (Wilson Fox). A marked increase of the vessel walls in an organ naturally tending to anæmia, such as the skin, can of itself never favour bleeding. Swelling of the walls of the subcutaneous arteries and the transitional vessels diminishes the blood pressure and the amount of blood in the cutis, and thus acts directly in opposition to other causes favouring bleeding. A swelling of the capillary walls directly produces a local anæmia, and in the neighbourhood no more bleeding than an anæmic tumour, such as a keloid or a scar.

The latter changes, according to Uskow (endothelial swelling of the

capillaries in scurvy) and Leloir (capillaritis desquamativa in petechiæ of the legs), the first-named, according to many authors, especially Hayem, Kogerer, and Mraçek, play a *rôle.* Hayem referred the bleedings of the skin in a cachectic phthisic and in a case of peliosis rheumatica to the endarteritis obliterans which he found. It is evident that in a process which in other cases always leads to anæmia, so widespread as growth of the intima—one has only to think of sclerodermia, cartilagenous initial sclerosis, lupus scars, etc.—an action favouring bleeding is only possible when the changes affect only certain arteries and the remainder are the more filled with blood, thus by means of collateral congestive hyperæmia; or if the growth chiefly or entirely affects the veins of the skin (endophlebitis obliterans) by means of stagnation hyperæmia; and in the latter cases œdema, diapedesis and a chronic eruption of petechia would be looked for. As the latter event can be excluded as in the highest degree improbable, there only remains collateral congestion as a possible cause of bleeding, if endarteritis obliterans must be blamed.

Kogerer also regularly found widespread endarteritis of the cutaneous vessels in hæmorrhages, with thickening of all the vessel walls, hyalin degeneration and areas of fatty degeneration, growth of the endothelium and narrowing of the lumen. Most severely affected were the largest arteries of the stratum reticulare, then the vessels of the fatty cushion, least the sub-papillary vessels. Kogerer does not directly ascribe the bleedings to these very grave changes, but through the medium of disturbances of the circulation and thrombosis. Unfortunately I cannot confirm his results, and apart from this the regularity of his discovery is most suspicious. May it not be that the so-called endarteritis obliterans is in many cases an abnormal state of contraction with folding of the intima and thickening of the media of otherwise healthy vessels? This objection is the more justified since in the special question of the origin of the hæmorrhages in congenital syphilis this point can be fully discussed among the authors. Certainly it was tempting, after the work of Heubner and others on the syphilitic diseases of the vessels, to ascribe the characteristic pupura of congenital syphilis also to vessel changes. But Fischl has already rightly protested against such an assumption, supported by no positive observation, and showed that the supposed hereditary vessel changes of the skin had been confounded with a greater degree of contraction of the vessels. These are, except for the rupture of the adventitia, at the seat of bleeding, absolutely normal. Schütz agreed with him, while Mraçek recently demonstrated on the small and middle-sized venules in hereditary syphilitic purpura, striking changes, nuclear growth and new formation of connective tissue, and he finds these the more developed

the greater the bleeding. But these results need not only confirmation with the precaution of comparison with neighbouring vessels and the exclusion of altered conditions of contraction, but also the as yet completely absent explanation of the mechanism of bleeding. For Mraçek ascribes the bleedings indirectly to the medium of venous stagnation, but overlooks the fact that other clinical and anatomical changes must have been present. A specific endophlebitis, if its isolated existence in hereditary syphilitic children should be confirmed, might well come into consideration in this case as favouring a rupture from some other cause. It is very indicative of the difficulty of a histogenetic explanation that, in the search for changes in the vessel walls which might favour bleeding, such are not found by which the vessel becomes thinned, tender and fragile, and thus directly disposed to hæmorrhage; but on the contrary, thickenings on the walls of different kinds, which are only available indirectly and with more or less distortion for a theory of rupture.

Secondly, *plugging of the vessels,* which plays so marked a rôle in hæmorrhages in internal organs, has been looked to as a cause of cutaneous bleeding, and the most varied observations have been brought forward in this connection. Kogerer again appears to have been the most lucky, for in his thirteen cases of cutaneous bleeding he never once failed to find thrombi in the veins, and he frequently found them also in the capillaries and in the arteries (mostly in the hypoderm). This regularity compared with the results of other authors and myself is most striking; but if we admit that no confusion with the simple dammed up blood has occurred, it is still to be noted that the thrombosis of a cutaneous vein by itself leads neither to bleeding nor œdema; the collateral anastomosis is too free. Only very wide-spread venous thrombosis of the skin could have such an effect if, at the same time, the supply of blood were normal or excessive. That where the skin arteries can contract, there is still no bleeding in the skin, we learn from the cases of thrombosis in the large veins of the leg which regularly induce œdema but never hæmorrhage; and erysipelas shows that very wide-spread venous thrombosis of the skin can exist with paresis of the arteries and without bleeding usually appearing. A satisfactory mechanical explanation of cutaneous bleedings is certainly not to be found in Kogerer's observations, nor in the more scattered ones of venous thrombi by other authors. In all these cases it is simpler to refer the thrombi either to the same unknown cause as the bleeding or to regard them as results of the bleeding, which both for the rupture and the neighbouring vessels is an obstruction to circulation of the first rank.

More numerous are the statements regarding *capillary emboli* and

thrombosis. Ollivier and Ranvier attributed the development of petechiæ in marked leucocytosis to collections of white blood corpuscles and capillary stasis. Fagge and Harris observed, in the cutaneous bleedings accompanying sarcomatous tumours of internal organs, a plugging of the capillaries with sarcomatous masses, and they regarded these as the cause of the bleeding. But particularly since Klebs found in a form of infantile purpura (hæmophilia acquisita neonatorum, Rittershain) bacterial colonies in the vessels, many bacterial emboli with or without consecutive capillary thrombosis, have been described in the most varied infectious and septic diseases (Cornil and Martin de Gimard, Eppinger, Petrone, Cohnheim, Weigert). Recklinghausen on the contrary sought in vain for capillary thrombosis in the spots of hæmorrhagic variola and the petechiæ of diphtheria and typhoid. If here the expected bacterial thromboses were not found, I only need to recall the complete stoppage of the papillary vessels with strepto and staphylo-cocci in every septic exanthem in order to show that conversely wide-spread infectious capillary thrombi do not necessarily cause bleeding. Opposed to those more scattered observations in different infectious diseases it has recently appeared probable that the bleedings in the true purpuric diseases are to be referred to emboli of bacteria and subsequent capillary thrombosis. Like Klebs in purpura neonatorum, Letzerich found in purpura hæmorrhagica chronica, characteristic bacilli embedded in a gelatinous plug, completely filling the capillaries, which he attributed to the action of the organisms on the serum albumen of the blood plasma. They are found chiefly at the angles of dichotomously branching capillaries and correspond to the frequently observed light spaces inside the petechiæ; they may be expressed in toto from the excised skin. Since then the discoveries of bacilli in purpura have increased from year to year, without the genesis of the skin bleedings on the basis of these new facts being worked at and cleared up in proportion. But the presence of bacillary emboli in purpuric diseases as such stands beyond all doubt and merits the most thorough consideration in any future theory of cutaneous bleeding.

A series of bleedings which up to now have been referred to simple fibrinous thrombi will certainly find a better explanation in these bacterial fibrinous thrombi. This is particularly so in the cases of Hayem, who ascribes the origin of the bleeding in purpura partly to the plugging of the arteries and capillaries with fine granulated masses which "par précipitation granuleuse" are spontaneously generated in the blood and form emboli. In the experiments on which he founded his view, ox serum introduced into the circulation of a dog induced hæmorrhage in the intestine, the spleen, the serous membranes, and at the seat of the bleedings the capillaries were plugged with viscous

hyalin, powerfully-refracting drops. But the cutaneous bleedings which would have been so valuable in the explanation of purpura were absent, and so the experiments of Hayem remain as valueless in the explanation of human purpura as the investigations in ferment intoxication and the development from them of hæmorrhages of internal organs, by Köhler, Angerer and v. Düring.

It is therefore never the embolus and thrombosis of the cutaneous vessels as such which leads directly to hæmorrhage; so far as we are familiar with the mechanism of the skin circulation these events are not sufficient to induce bleedings in the skin in the same way as they regularly do in, *e.g.* the intestine, the retina, and on the serous membranes.

There must always be in addition a particular chemical influence, which may arise from sarcoma masses or bacteria, nor is the presence of any kind of pathophoric, parasitic bacteria alone sufficient; they must be definite micro-organisms which specifically influence bleeding. Only the emboli of such induce—at least in purpura—either the bleeding directly, or they prepare the ground, so that an otherwise insufficient trauma induces the bleeding. But if it is so, then comes the question whether a plugging of the arteries, capillaries and veins is necessary for the induction of this bleeding, whether it must go the length of the obstructing, gelatinous, fibrinous thrombosis around the foreign body or whether the presence of this last in the skin vessels is not alone sufficient to cause the bleeding? We may at least allow to the simultaneous stoppage of the vessels the rôle of a predisposing factor. But the specially fibrinous inflammations of the skin, Erysipelas, progressive Phlegmon and Elephantiasis nostras present far more wide-spread thromboses of the vessels than we usually see, and yet they have no tendency to hæmorrhage. So the much-discussed chapter of embolism and thrombosis in cutaneous bleeding is reduced finally to this, that there are poisonous foreign bodies, in particular certain bacteria, whose entry into the circulation of the skin, in some unexplained manner and without the necessary intervention of wide-spread thrombi, induces hæmorrhages.

To the same category belong all those bleedings which were formerly supposed to be due to "Blood dissolution" and with these were reckoned the septic bleedings, hæmorrhagic Small-pox and the petechiæ appearing during other acute Exanthems. Although in a certain sense the old views of humoral pathology are at the present day once more raising their heads, in that, stimulated by the discovery of toxic bacterial proteins the action of highly complex organic combinations with healthy and diseased tissue produced by the body itself is being eagerly studied, the humoral idea of a dissolution of the blood

has no prospect of being restored. For according to it the blood would as a whole, by some chemical change, acquire the power of penetrating the vessels, while we to-day ascribe the bleeding certainly also to a chemical poison in the circulation, but connected only with the seat of the bleeding, and sharply localised at definite points of the vascular system. There is certainly in a thus limited chemical action a means (organised) of conveyance of the poison, such as we have in the emboli of bacteria and the embolic masses of sarcoma. In the petechial forms of the acute infectious diseases (acute exanthems, miliary fever, yellow fever, typhoid, typhus, cholera, diphtheria, puerperal fever, ulcerative endocarditis, Cerebro-spinal meningitis, plague), this explanation would also be available. But it may be objected that for the petechiæ in chronic Bright, articular rheumatism, icterus gravis, severe malaria and Leukæmia, it is less applicable, and for the bleedings which are caused by pure chemical intoxication (Sulphuretted Hydrogen, Phosphorus, Iodide of Potash, Snake poison) not at all. In these chronic diseases bodily elements are certainly possibly the conveyors of the poison, and also in the latter, apparently pure intoxications, not altogether to be cast aside, without falling back on the old vague definitions of dissolution of the blood. Firstly, it is possible that the chemical poison (PH_2S) produces, in the vascular system or other organs, areas of degeneration products which may become emboli, or they may prepare the ground for bacteria, and first make possible their entrance into the circulation. With regard to Pot. Iod. it must be borne in mind, that it is usually given as a remedy in chronic infectious diseases such as syphilis and rheumatism, and in such cases the Iodine purpura is possibly no simple intoxication. Altogether these cases are so problematic and so rare that we will do well to clear our ideas on the genesis of cutaneous bleeding from other examples.

Auspitz first pointed out in his interesting researches on venous stagnation by means of the cupping bandage, that a high degree of venous stagnation alone is sufficient to induce in healthy skin macroscopically visible escapes of blood, in the form of red to blue black, very fine petechiæ. These are chiefly located in the neighbourhood of the bandage in the bend of the elbow. But these bleedings are the only ones which, experimentally induced on man, have an undeniably diapedetic character. They appear within the vermilion stagnation spots, that is, where already for a long time hæmoglobin-containing serum has been pressed through the wall of the distended capillary, and are, as Auspitz has already pointed out, to be considered as the analogues of the diapedeses induced in animals by Stricker and Cohnheim. Their peculiarity consists in their gradual formation and

remarkably small size. Of the hæmorrhages induced by trauma and vessel rupture, the tiny escapes of blood induced by the stings of fleas and other insects resemble them, but they are deeper in the skin than these. If we look for analogous cases among the spontaneous ecchymoses on the basis of venous stagnation, we find them at most in certain tiny chronically-appearing spots on the legs in long-standing stagnation accompanied by sanguinolent œdema. What is developed by the forcible compression of the cupping bandage in a quarter or half an hour appears here very gradually in the course of weeks or months. Especially is the neighbourhood of callous ulcers affected by these imperceptibly increasing diapedetic ecchymoses, in which an ever-deepening pigmentation from blood pigment developes.

But even these none too common cases, which pretty well confirm the experiment, show that the acute outbreaks of purpura, even when they occur on the leg, cannot be referred simply to a stagnatory diapedesis. They appear suddenly over night, and are at once the size of a mustard seed to a lentil. Even universal cases of purpura of the most different forms show a preference for the dependent parts of the body ; the spots appear first and most freely on the leg, and there is no question but that the stagnation as such has a favouring influence on these bleedings due to rupture, since it alone can, under circumstances, cause diapedetic hæmorrhages. The question is rather whether a stagnation can of itself lead to rupture of the skin vessels.

We must next note that thrombosis of the large veins of the leg, while in virtue of venous stagnation regularly leading to œdema, hardly ever induces cutaneous bleeding. Very rare exceptions only prove this rule ; Rayer saw in a case of thrombosis of the right illiac vein, thirty hours before death, the right leg become œdematous, and twelve hours before death become dotted with petechiæ and suffusions.

But we must not overlook the fact that the stagnation of blood in the leg is not a pure stagnatory hyperæmia, such as gravity can induce on amuscular flabby parts. But there exists in all cases a relatively increased vessel tone which leads to the arrest of the *vis a tergo*, to an abnormally low blood pressure in the veins of the leg, and thus finally to a backward movement of the blood column in these last ; hypostatic hyperæmia. That this last alone no more induces bleeding by rupture than the stagnation alone, daily practice teaches. The falling blood column dilates the larger and then the smaller veins, distends the valves, induces varicose swellings, lengthens the veins, produces coiled packets of veins, finally overcoming the venous valves, reaches the skin veins, dilating them into worm-like strings which make the cutis swell up like a cushion—all this without concurrent bleeding from rupture of the veins. For there exists all the time the increased arterial tone

which limits the blood flow to the dilated veins in the normal way.

But these circumstances immediately change as soon as the vascular tone is diminished ; it may be that an inflammatory hyperæmia appears, or—*ante mortem*—a simple vascular paralysis. Then the skin veins are subjected to increased pressure from both sides, they dilate and finally yield. So we frequently see wide-spread ecchymoses appearing on varicose legs, if a hyperæmia of the skin is set up, from an injury or prolonged intercurrent eczema, while for years the hypostatic hyperæmia showed no tendency to bleeding. The escapes of blood in the death agony on dependent parts (back, legs) seem to arise in the same way, if the diminishing power of the heart favours a hypostatic hyperæmia and vessel paralysis set in at the same time ; and this tendency to agonal purpura is further increased if a general venous stagnation—in diseases of the heart and lungs—has already led to overfilling of the peripheral vessels.

It is not then in stagnation alone, but in its combination with hypostatic hyperæmia, and in the combination of this latter with any form of congestive and paralytic hyperæmia, that we have to seek for a sufficient ground for the over-distension and rupture of the cutaneous veins. Many other bleedings have a similar complex etiology. When, for example, in an iodine purpura the petechiæ appear only on the leg, the mechanical over-distension of the cutaneous veins by the force of gravity is, in addition to the action of the iodine, certainly concerned. And it is no accident that the bloody suffusions of scurvy usually begin on the calves and at the side of the achilles tendon, and the spots of purpura simplex on the legs and fore-arms. Whether "nervous purpura" (Couty) is to be considered as a stagnation hæmorrhage caused in this way by venous spasm with relatively wide arteries, or whether it chiefly ensues through rupture or diapedesis, further investigation must show. Strauss found in tabetics during neuralgic crises, petechiæ over the painful points. Faisans also noted cutaneous bleedings in ordinary neuralgia corresponding with the painful spots. The small petechiæ accompanying spastic œdema in the course of many cases of angio-neuroses (urticaria, erythanthema) appear, from those investigated, to be diapedetic.

Before we conclude this short review of the true and probable, remoter causes which relate to the hæmorrhages due to rupture, we must consider an affection of the whole vascular system, which, as a congenital abnormality, fills an isolated place among the preparatory tissue changes ; Hæmophilia. Schönlein discovered, and he was confirmed by other authors, that in this condition the vessel walls are extraordinarily thin. It is found, as is well known, mostly in the

male members of certain families hereditarily affected with this disease, who possess a thin, feebly-pigmented skin and fair hair. Cutaneous bleedings are said to occur in such, spontaneously, without any external cause. It is at least certain that every, even the slightest mechanical injury, causes severe external hæmorrhage or enormous blood boils. Prolonged pressure on one place in lying or sitting may readily induce blue patches and hæmatomata. The difficulty of stopping the bleeding from the smallest wounds of the skin, which has been proved not to depend on faulty coagulation of the blood can only be due to a want of retraction and elasticity of the cutaneous vessels, and as the thin-walled condition of the vessels of the cutis themselves is already distinct we will hardly go wrong if we assume a deficient wall formation in the subcutaneous tissue. Indeed a defect of the musculo-elastic system of the hypodermic vessels must increase very markedly the place of least resistance in the cutaneous vessels. Here then the investigation of hæmophilia should commence.

If we now sum up how far the already observed or otherwise concluded preparatory tissue changes may be looked upon as truly favouring the rupture, there remains to us only very few sufficient and likely results. We must completely give up the much quoted theories of mechanical stoppage of the vessels, be they caused by thickening of the walls, growth of the intima, swelling of the endothelium, thrombosis, capillary emboli or anything else. Only the *emboli* of *specific, hæmorrhage-inducing bacteria* remain as a promising hypothesis. From the theory of a particular fragility of the vessel walls, all that we have definite is the *congenital defect* in the *walls* in *hæmophilia.* Of the class of causes which may be indicated in general as stagnatory it is clear that the ordinary forms of stagnation * supply some but no sufficient cause for cutaneous bleeding through rupture of the vessels, but that they may do so *in combination with one another or with simultaneous paralysis of the vessels*, and that *hypostatic hyperæmia*, of all forms of hyperæmia, possibly plays the most important preparatory rôle.

If we now enquire further how these different anatomical facts stand in relation to the mechanism of rupture as we have previously explained it, the factor of potential stagnation in the deep cutaneous veins is certainly an equally plausible cause of rupture, as the hypothetically assumed deficiency in elastic contractile elements in the subcutaneous vessels of bleeders. But the bacteriogenic bleeding cannot be adopted in the above sense without something else; for its explanation, there must be discovered a force--perhaps chemotactic—

* Apart from the traumata of sucking and pinching mentioned at the commencement.

which causes an unknown form of movement of the blood corpuscles. Equally obscure are the bleedings caused purely by chemical agents (K, I, P, H_2 S), while the agonal and neuropathic petechiæ, are perhaps different forms of potential stagnatory hæmorrhage and thus may be explained by the mechanical view. At all events, in every future case of rupture one must enquire what particular circumstances and forces caused it in that particular case. The more our knowledge of the domain of rupture has extended, the more limited has become that of diapedesis. We will do well at present to recognise diapedetic petechiæ with certainty only where the circumstances closely correspond to those in Auspitz's experiment, where fine red or blue points like flea-bites slowly appear on a grey-blue ground, betray no tendency to rapid increase and confluence, and where here and there a spot of vermilion indicates the escape of serum, containing hæmoglobin. Moreover, these vermilion spots are always a sign of increased vessel tone, they are not present in well-marked paralysis of the vessels nor in severe stagnation (for example not in scarlet fever), and their absence is quite compatible with the appearance of diapedetic bleedings. These conditions are indeed found in many under extremities affected with general stagnation. And these minute escapes of blood are also present in many angioneuroses, certain cases of urticaria, in other erythanthems, particularly of the fore-arm and leg, and finally also in the true erythema multiforme of Hebra. In these cases the stagnation as well as the spastic œdema and the vermilion red appearing with it are the results of an abnormal irritability of the vessel muscles and the predominance of the venous narrowing.

But the domain of diapedesis is considerably widened if we expand somewhat the definition of the diapedetic cutaneous bleedings. On the one hand it is clear, since the chief cause of diapedesis, stagnation, is also a chief assistant cause in rupture, that many cases must exist in which the outpouring and the filtration of blood are closely related and pass into one another. On a leg showing diapedesis, rupture is developed more easily through new additional circumstances, because many of the cutaneous veins are already over-filled with blood. Therefore, where stagnation comes into consideration (*e.g.* also in cupping), the domain of diapedesis passes insensibly into that of rupture.

Thus there are in very many cases microscopic diapedeses which completely escape macroscopic recognition because they are too small. Indeed, while in looking over perhaps ten or twenty cases of escapes of blood, macroscopically recognisable on the corpse, only one will be found to have arisen through diapedesis, we come across, in a whole series of inflammatory, and often also non-inflammatory skin diseases, tiny

collections of blood in the cutis, which can only have arisen from diapedesis. The same may be seen in scarlet fever, measles, small-pox, in acute eczema, and even in warts, pointed condylomata, malignant tumours, in short, in the most heterogeneous dermatoses, and without necessary relation to the respective processes. If one enlarges the definition of the diapedetic cutaneous bleedings to include these equally common and accidental discoveries, and separates them completely from the clinical diagnosis, their domain is perhaps even larger than that of the rhectic bleedings. In these last cases the diapedetic origin is proved by the small quantity of blood corpuscles; a tear in the wall always leads to larger pools of blood. But even the larger petechiæ, due to filtration, can, apart from the absence of any rupture, be recognised by the fact that the blood corpuscles are distributed in the tissue along the blood-vessels, dendritically separated, and form less compact masses. I had at one time hoped to find in the amount of fibrin some indication of their manner of development. Since in rupture we have the whole blood, and in filtration a lymph rich in red corpuscles, poor in white corpuscles and albumen, we might expect a difference in the tendency to coagulation, the more, as there is a widespread idea that the blood coagulates in the tissue as soon as it leaves the vessels. Winiwarter states that the outer parts of a blood coagulum in the skin are coagulated. But with Weigert's fibrin stain I have never found fibrin in any form of cutaneous bleeding, except in a case of bleeding in the track of a subcutaneous injection, where the blood was manifestly in contact with the external atmosphere. But the results were different on the application of my methyl blue tannin fibrin method, which, in addition to the fibrin filaments demonstrated by Weigert's stain, specially stains granular fibrin. With it we find in most cases large quantities of granular fibrin. In the larger pools of blood there is usually a peripheral zone, which contains blood corpuscles more scattered, but between them innumerable granules of fibrin. The latter are to be recognised through the whole extent of certain bleedings.

The expectation that this form of fibrin was possibly limited solely to the rhectic bleedings has not been fulfilled. It is found in cases of infectious purpura, and in pre-agonal and stagnation bleedings in some cases abundantly, in others sparingly, and also in diapedetic bleedings. Its more or less extensive presence depends, in the first place, not on the manner of the escape of blood, but on the quantity of tissue lymph, which escapes at the same time. But this varies in every case, indeed in every phase of bleeding. Around the larger blood pools there is usually a zone rich in serum with marked precipitation of fibrin, but even in the smallest diapedetic bleedings a rich

serous transudation with the familiar granules may at the same time appear. Most striking is the amount of these granules in small hæmorrhages which occasionally appear in the infectious processes with a tendency to coagulation of the exudation, such as Anthrax. Here the presence of relatively small masses of blood corpuscles is quite irrelevant compared with the quantity of the tissue lymph which alone has the power of coagulation. The presence of these granular masses always indicates that the filtered as well as the poured-out blood can coagulate in the skin tissue, although in an unusually loose manner; the ordinary appearances of coagulated blood are absent in the interior of the cutaneous tissue.

Thus we have very few criteria for the definite diagnosis of diapedetic cutaneous hæmorrhage. The absolutely convincing observation of red blood corpuscles passing through the walls of capillaries and veins I have not yet been able to make; and I believe that this rigorous postulate has not yet been fulfilled by any investigator. Consequently the negative observation of the absence of a tear in the vessels, since this became more easy and more certainly recognisable, has increased in value. Where, therefore, one finds on horizontal sections of the deeper cutis margin no ruptured cutaneous veins, where the amount of blood is not great and only present in the neighbourhood of the vessels, where the escaped blood is seated only around the better protected superficial skin vessels in the papillæ, or even only in the epithelium, where other appearances of stagnation, such as the presence of hæmoglobin in the lymph and œdema, can be recognised where, therefore, the assumption of an external injury is inadmissible, then we must in the present state of our knowledge assume the existence of a diapedetic bleeding. That the detection of the corpuscles in the act of escape from the vessel walls is difficult, and as yet impossible, is not to be wondered at. Both the capillaries and the blood corpuscles are smooth and elastic, and resume immediately their original form after their escape. Wagner found in cutaneous bleedings due to squeezing, blood coagula so embedded in the epidermis that their connection with ruptured capillaries could not be recognised, and the way by which they had reached the epidermis was not even indicated by scattered blood corpuscles. This observation, which I can personally confirm, speaks for the ready dislocation of the very elastic blood mass inside the lymph spaces of the tissue, and warns us to be cautious in the classification of small superficial hæmorrhages. Here, in the superficial capillaries the absence of a recognisable rupture does not, as in the larger veins, exclude the possibility of vessel rupture.

However the bleeding has occurred, the blood corpuscles remain lying in the lymphatics of the skin, while the blood serum under

pressure of the tissue extends further outwards, and is more or less rapidly taken up by the lymph and blood-vessels of the periphery, so far as it does not, as in certain cases, undergo a loose coagulation. If the bleeding is inconsiderable, only the lymph spaces in its immediate neighbourhood are dilated, and the lymphatics filled with blood corpuscles. If the bleeding is more considerable, there is in the centre a loosening and tearing of the collagenous bundles. The mass of blood is driven in the direction of least resistance; in rupture of the veins on the under surface of the cutis where it is most frequent, partly toward the subcutaneous tissue, partly outwards into the cutis, into the large lymph spaces sheathing the blood-vessels. Consequently the greater part of all cutaneous bleedings show the hypoderm permeated by a net-like collection of blood corpuscles, hanging together and sheathing the fat lobules, quite a long way from the place of rupture. If by this means a tenser filling of the hypoderm has ensued, and if the bleeding still continues, there is usually found in the under part of the cutis a large pool of blood, in which the collagenous and elastic tissue is torn and rooted up in streaks, and penetrating nerves and vessels are dissected out and separated from their surroundings. At the same time, from the increasing tissue pressure, many capillaries and veins which are in the region of bleeding, without being torn, are narrowed and partly completely pressed together, and thus the disturbance of circulation is not limited to the ruptured vessels, but there is in addition an irregularly distributed anæmia, and stagnatory hyperæmia, which not a little hinder the absorption of later blood coagula. On the other hand, the increasing tissue tension also tends to the closure of the torn vessel by the bleeding itself. Stasis ensues from the place of the coagulation outwards, and permits the closure of the torn spot until the torn vessel is definitely scarred.

The petechiæ stretching from the subcutis margin into the cutis are always more sharply limited microscopically in the latter than in the subcutaneous tissue, in that the more rigid cutis penetrated by narrower lymph spaces is compressed by the increasing bleeding to a wider extent, and thus the extension of the blood into the neighbourhood is always becoming more difficult. But only the blood corpuscles are firmly held together by the pressed asunder and much distended cutis tissue, while the blood plasma is filtered off, and for some time surrounds the mass of blood corpuscles as an œdematous halo. There is also combined with the bleeding, when it follows stagnation, a diffuse œdema of the neighbourhood to which the compression of neighbouring veins and the circumscribed central stasis, which follows the rupture, may contribute its share. In bleedings which develope

from pinching of the skin, a spastic œdema of the neighbourhood, which cannot be pressed away, often concurs in addition, and is due to a direct increase of tone of the co-affected neighbouring vessels.

The small bleedings of the papillary body and the epithelial bleedings are usually traumatic, arising from squeezing or superficial wounds, and appear either in the healthy skin or very often in those structures, such as warts and cutaneous horns, which by their projecting from the surface of the skin are more easily injured. The bleeding is usually primarily in the papillary body, or between this and the epithelium. If only a small part of it is in contact with the prickle layer, this tends to grow around the mass of blood and to sequestrate it from the skin. It is then removed *in toto* from the upper surface of the cutis, and forms for a long time a red spot on the skin, being finally exfoliated, "born."

In other cases the epithelial bleeding presents itself as a secondary hæmorrhagic change in epithelial degenerations not primarily hæmorrhagic, particularly in vesicular, pustular, and bullous dermatoses, such as Variola, Varicella, Zoster, Herpes iris, Pemphigus, and Ecthyma. This is only rarely due to trauma, but usually to a complication with stagnation or infectious purpura. But all causes of bleeding certainly do not make the above epithelial degenerations hæmorrhagic, for Auspitz was unsuccessful in filling small-pox and ecthyma pustules with blood by inducing stagnation, although petechiæ were developed in abundance. It evidently depends in given cases very much on the power of resistance of the epithelial layer immediately covering the papillæ.

Only very rarely does the blood escape through the externally unwounded skin. In these cases we have to do with bleedings which find their way into the lumen of the coil glands and appear as bloody sweat. It is usually found in nervous females who suffer from some form of cramp (v. Franque). Severe pains and a feeling of tension of the affected part of the skin precede the bleedings and disappear with the advent of bleeding; they most commonly appear on the forehead, breast, axillæ, and hands, and sometimes unilaterally. Hæmophilics occasionally show such a hæmatidrosis.

Only the blood masses which reach the epithelium retain unchanged their red colour, and either on this account or from their persistence, may be confused with small angiomata. There is no lymph present to dissolve them. In the cutis, on the contrary, there begins, very soon after the occurrence of the bleeding, solution of the hæmoglobin, which is partly re-absorbed with the blood plasma, and partly crystallised in the tissues (precipitated). The remains of the cells swell, break up, and are also absorbed. Where large masses of blood corpuscles are

closely packed they break up, without previously giving up their hæmoglobin, into yellow or brownish flakes, which are gradually converted into pigment granules, and as such are partly taken up by the connective tissue cells.

Very rarely the bleeding has another fate, termination in encapsulation and cyst formation, and this only when from the commencement the surrounding tissue is powerfully compressed, and afterwards the movements of the skin which favour absorption remain in abeyance. The contents of the cyst are serum, containing hæmoglobin and pigment mixed with granular detritus of blood corpuscles.

The escaped blood presents during its resorption a series of characteristic colour changes on the surface, which have nothing in common with the colours of the rainbow, but are caused by the superposition on red blood masses and yellow hæmoglobin-containing serum of colourless but opaque media. Only in very superficial petechiæ does the colour change from red into a faded yellow and finally into a pale brown. Deep-reaching, and therefore, according to Göthe-Brücke's law, apparently blue hæmorrhages shimmer green in the centre through the yellowish hæmoglobin-containing periphery, and pass in the middle from blue through green and yellow into brown, on the border from yellowish-red into brownish-yellow.

Finally, there remains in a collagenous tissue loosened by the bleeding a larger or smaller quantity of pigment, partly free, partly enclosed in cells, which gives to the skin a dirty brown or, if more deeply seated, a greyish colour. After repeated bleedings the skin becomes dark brown or dark grey, but never so black as in epithelial pigmentation and the melanoses.

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Section II.

INFLAMMATION.

The definition of inflammation as one of the most important and common of the affections of the skin has been transferred to general pathology. It might be thought that here at its source it could be sharply and comparatively easily defined, and that the well-known difficulties of a limitation of the definition in general pathology were attributable, solely to the very great differences in different organs, for indeed it is hardly possible to imagine greater differences than, for example, between the inflammatory conditions of the serous membranes and of the central nervous system. But just here on the skin this difficulty is present in particularly high degrees, simply because the numbers of those affections of the skin which are attributed to inflammation by far exceed those of all other organs. If we exclude tumours of the skin and a few other affections, all the other dermatoses have been at one time or another ascribed to inflammation. It is not to be wondered at then, if in the pathology of skin diseases the pure anatomical principle of division so far as regards inflammation has been mostly forsaken, and in most text-books a slip-shod arrangement of the clinical forms has taken its place. Instead of a division into fibrinous, purulent, hæmorrhagic, etc., inflammations, we find one into erythematous, papular and bullous eruptions. Or we too often see, with a total neglect of any rational pathological scheme, scarlatina and urticaria, eczema and small-pox, psoriasis and erysipelas, syphilis and favus ranked alongside each other.

This general avoidance of a thorough scientific investigation of the finer details of the very varied conditions of inflammation in the skin, is as easy to explain, as it is difficult to overcome. We can only, step by step, reach a better position, and therefore the following attempt at a more accurate subdivision of the inflammations of the skin from the anatomical standpoint, deserves careful attention. Mainly on the side of the pathologist, for to admit it at once, I consider, in the present state of our knowledge, a *pure* pathologico-anatomical division of the greater number of these most varied affections *absolutely impossible.* It would not only not promote pathological clearness, but rather obscure it if one, for example, were to group together all the fibrinous inflammations of the skin, and thus to put in one group burns of a certain degree, zoster, erysipelas, certain eczemas and varicella, while in another group there appeared burns of another degree, other forms

of eczema and small-pox. We reach equally ridiculous results from whatever side we seek to make our divisions with the familiar pathological or anatomical formulæ, and it is very soon evident that it is the ignoring of etiological factors, which revenges itself in the combination of dissimilar or the separation of similar examples.

If we use this etiological factor as a principle of division we can already rationally divide inflammations into certain groups of diseases, which should satisfy not only the clinician but even the pathological anatomist. The reproach which is made against every etiological division, from the anatomical standpoint, that one and the same cause may produce the most different results (for example different degrees of heat), and again that different causes on the same organs may induce the same, is only true to a limited sense. Indeed the skin with its innumerable forms of disease shows most clearly that, with sufficient study, every different effect has a different reaction on the organism, and especially the infectious inflammations of the skin, daily becoming better known, indicate the enormous differences in action of infectious agents morphologically related, such as ringworm and favus, syphilis and leprosy. But in addition, the parasites of the skin may as truly be considered anatomical as etiological factors. Where we already know the distribution of the parasites inside the skin, this knowledge immediately conveys a better comprehension of the whole process, and its pathological anatomy becomes impossible without due regard to the relationship between the tissue and the infectious agent. The infectious inflammations of the skin form so great a majority that the principle of division adopted may be unhesitatingly transferred to the whole class of inflammations. But the main characters of the group must always be so chosen that they allow us to recognise a direct and constant relation to definite anatomical peculiarities of the affections belonging to the group, and I will have to show that this is the case in the division which I have chosen.

This relation is most evident in the **infectious** inflammations of the skin and these present an instructive sample of the other inflammations. The next division of this great group is supplied by the seat and the spread of the infectious germs; on the one hand in the whole organism and on the other in the skin alone. Thus we distinguish *local infectious diseases of the skin* and *general infectious diseases* with *symptomatic disease* of the *skin* (small-pox, scarlet fever, measles, etc.).

The further sub-division of the first very extensive group is according to the special seat of the medium of infection in the skin, and first in two chief groups, according as the germs found (or their presence assumed) are in the *epidermis*, or *in the cutis*. With the epidermis

we of course consider also its appendages, hairs and nails. This anatomico-etiological principle of division provides us with natural groups of diseases. The great group of cutaneous catarrhs, which are every day more recognised as a natural group, correspond completely with the group of "*local infectious diseases of the skin with the seat of the infectious germ in the epidermis.*" Only through their limitation to the cells of the epidermis do we understand the anomalies of cornification (parakeratosis) invariably combined with them, the commencement of the inflammatory changes of the cutis at the epithelial margin, the persistently superficial and therefore usually benign character of the affections and the absence of a tendency to attack the hypoderm and internal organs. Even the purely pathological characters of the group harmonise with the epithelial seat of the germ; for it is evidently due to this, that only the slightest forms of inflammation, the serous, sero-fibrinous and purulent inflammations are met with in this group. Indeed in many the exudation is so insignificant that it hardly reaches a recognisable quantity of exudation, and the inflammatory effects are only evident in the growth of the cells, especially in the growth, the hyperplasia, of the prickle cells, and their proliferation (Acanthosis). I do not hesitate for a moment in regarding this swelling of the epithelial cells and their active growth, as a slight degree of inflammation, a true parenchymatous inflammation of the prickle layer, induced by epithelial infection. According to the quantity of recognisable exudation, or the greater prominence of epithelial degeneration on the one hand and epithelial proliferation on the other, two processes which do not exclude one another, but rather are always increased though in different degrees, the ultimate sub-division of this class of dermatoses is into *moist* and *dry cutaneous catarrh:* into "Eczematosis" and "Parakeratosis." The idea of the last grouping is, as is evident, purely pathological.

More severe and malignant forms of inflammation meet us at once in the *local infectious inflammations of the skin with the seat of infection in the cutis.* And here naturally there is much greater variety of form.

Opposed to the very few simple *serous and sero-fibrinous inflammations* (progressive phlegmon, erysipeloid and erysipelas), most of the affections in this category belong to the *purulent* and *necrotic* inflammations: Furuncle, Panaritium, Phlegmon, Ulcus molle, Anthrax, Carbuncle, Glanders, Actinomycosis, etc.

Closely related to the infectious inflammations of the skin proper is the important and significant division of the so-called granulomata, which have recently and properly been generally separated from the tumours proper as the "infectious granulomata." They are so nearly

allied to the infectious inflammations of the skin, and bound to them by so many transition forms, that properly only the tendency to growth, more or less present in all, justifies their separation. To the clinical relationship which strikes one at once in *e.g.* a comparison of soft shanker with the initial sclerosis, or gumma with furuncle, the histological corresponds, and we shall do well to rank the group of granulomata in our series as the fourth (growth-forming) division of infectious inflammations of the skin, the infection having its seat in the cutis. A second main division of the inflammations, that of the **neurotic,** is much more obscure both individually and generally. Under this name I unite a small number of inflammatory diseases of the skin which certainly among themselves differ very much; still all present a *definite relation to the nervous system,* or rather, we can as yet only explain the peculiarities by assuming a specific nerve influence on the course of the inflammation. On this ground they cannot be so simply and completely understood as the infectious or traumatic inflammations, as due to the simple presence of an excitant of inflammation in the skin, although most (if not all) of them may also be ascribed to infectious causes. But in some way, which must be further investigated, this cause requires the assistance of the general interposition of the nervous system, and this last stamps not only the clinical, but, what here alone interests us, also the anatomical appearance of these affections with peculiarities which seem to demand separate classification of these diseases. But I do not conceal for a moment that the crowding of this class of inflammations is merely provisional, and hope that by transference of many of them to the class of infectious inflammations it will be in time better limited and defined.

The relation of the dermatoses here concerned to the nervous system varies according as a neuritic or angio-neurotic character predominates. Among the neuritic inflammations are Zoster, Herpes progenitalis, and Labialis, and, as a chronic neuritic dermatosis, Hydroa (Dermatitis herpetiformis, Duhring). As true angio-neurotic inflammations, may be considered Erythema multiforme Hebra, Erythema nodosum, the neuro-syphilides and neuroleprides (Unna) and the prurigines. Anatomically the first present the fibrinous character, but differ from the infectious diseases most nearly related to them, *e.g.* Variola, in their anatomical distribution along nerve tracks and the implication of these last. The latter inflammations belong to the serous and hyperplastic, and approach on the one side the inflammatory forms of the angio-neuroses; on the other, the infectious growths (granulomata). The angio-neurotic character is evinced by the fact that the appearances of inflammation are almost exclusively limited to the immediate neighbourhood of the vessels.

Much more comprehensible in its etiological relation is a third class of inflammations of the skin, namely, those induced **traumatically,** the specially so-called *dermatitides.* One may conveniently divide them still further according to their etiology into mechanical, thermic and chemically-induced inflammations. But as clear as is the genesis of this process, so extraordinarily varied are the minute pathological processes and not only among inflammations caused by different traumata, but among those caused by simply quantitative gradations, there are present the very greatest differences. Thus, for example, the influence of a certain temperature leads only to paralysis of the vessels, a higher temperature leads to serous inflammation, and a still higher directly to necrosis. So that if we were to judge of these pathological conditions solely from one individual, anatomical appearance, the combustion dermatitis alone would have to figure three times, namely, under the disturbances of circulation, the serofibrinous inflammations, and the necrosing inflammations. To this there could be no objection had these anatomical pictures nothing else in common, which by their separation into different chapters would be lost. But this happens to be the case, not only in burns, but in all traumatic inflammations.

These are all caused by agents with an unlimited power of gradation, and which, coming from without, have an action, sometimes circumscribed, sometimes widespread, now superficial, now extending deeply, here weak, there energetic. Therefore we find anatomically in contrast to the infectious and neurotic inflammations a certain want of limitation of the inflammatory processes to the original margins of certain parts of the skin, a spreading in layers which is in proportion only to the traumatic factor.

So that—and herein lies the main difference from the local infectious diseases—we are dealing almost always with a single and more or less powerful interference in the economy of the skin, to which either an equally acute reaction, or a longer inflammatory and reparatory stage responds. But the whole process induced by trauma has always a typical course and conclusion. The difference is of importance chiefly in comparison with the infectious catarrhs, especially with the eczemas, with their etiologically well-grounded unlimited course; for even yet most of the artificial dermatites are wrongly called eczema.

In connection with this peculiarity of their course there is a third characteristic property of the traumatic inflammations. Two more or less definite periods may be recognised, that of passive injury of the skin, and that of active reaction. Particularly the more severe traumata, burns of a high degree, and caustics, present, in this sense, most instructive appearances. Where the traumatic influence is slight these periods are indistinct, owing to the slight impression of the

primary lesion; this is usually the case in the infectious and neurotic inflammations. Only those infectious inflammations which are caused by relatively powerful infections, such as the catarrh of scabies and tricophytosis, approach, in this connection, the majority of the traumatic inflammations.

In these peculiarities of the latter lies the reason for placing them anatomico-pathologically in a separate class.

In establishing this third class of traumatic dermatitis I must not omit to point out that most probably all of the processes in it comply with the chemotactic theory of inflammation, just as do the infectious inflammations. That is "eo ipso" clear of the chemical traumata. A granule of cantharidin and a growing filament of the tricophyton fungus have exactly the same result; a serous vesicle. That along with thermic influences there are concerned chemical actions proceeding from the products of decomposition of the destroyed tissue, is most probable. Without some such assumption the appearances observed could hardly be explained. And thus the only inducers of inflammation which do not fall in with the chemotactic theory are the simple mechanical traumata. And in this group everything is doubtful, both the enrolment of the few affections as inflammations and not rather as circulatory disturbances, and the explanation of the changes as being more simple. The more we have learned of the rôle of infectious agents in all inflammations of external wounds, the more has the number of simple traumatic inflammations decreased. Possibly the intertriginous inflammations, the ingrowing nail, are only circulatory disturbances until some external infection makes the process inflammatory.

This circumstance, its near relation to the disturbances of circulation, and not any special simplicity of the process, which does not exist, is the reason why I place the mechanical traumatic inflammations before all the other groups.

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A. TRAUMATIC INFLAMMATIONS.

1. Traumatic inflammations from mechanical causes.

This first category of inflammations at once gives rise to the consideration, whether we should place here all these conditions due to mechanical causes which previously without further consideration passed for inflammations. The antiseptic era of surgery has taught us

that a whole series of them are infections which have nothing to do with the mechanical injury as such. If we separate all these infectious diseases of the skin, there remain not many purely mechanically-induced forms, and even these must be carefully tested as to their inflammatory nature. On the other hand it can hardly be doubted that by single or repeated blows, bruises and bumps, pinchings and friction of the skin, a condition of true inflammation of the skin may be produced, with swelling, hyperæmia, increased heat and tenderness, without any lesion of continuity of the epidermis or the inoculation with organisms. In the sense of Cohnheim's theory that is self-evident, for the pre-supposed primary injury of the vessels may be equally well induced mechanically, as thermically or chemically. But according to the narrower limitation of the definition of inflammations given above, as an exudation process chemotactically produced, it appears doubtful whether we should regard these conditions as inflammatory.

I would hold it an important objection against any purely chemotactic theory of inflammation, if these swellings of the skin after severe blows, pinching, or squeezing, were on that account to be excluded from the inflammations. But this does not appear to me to be at all necessary. In weaker mechanical actions we have to do mainly, only with vasomotor disturbances, with swellings of the healthy skin analogous to those which slight irritants cause on pre-disposed skin (urticaria factitia). These phenomena pass over rapidly and without leaving any trace. In more severe traumata, there certainly ensues immediate necrosis of some of the more delicate elements of the skin, and thus material is provided which must be absorbed, for which purpose leucocytes must leave the vessels. This work of resorption may run its course without any macroscopically evident phenomena of inflammation, as we can observe in many daily surgical proceedings; every subcutaneous discision, indeed every subcutaneous injection leads to similar conditions. But the matter is otherwise when in this way multiple elementary necroses suddenly appear in a skin which is at the same time the seat of vasomotor disturbance, congestive and stagnatory hyperæmia. Particularly by the latter, can the work of re-absorption be disturbed and prolonged, and the repair of the circulatory disturbance made more difficult, so that there results a macroscopically evident exudation, which may remain in the tissue days or weeks.

As it is only the most severe lesions which call forth this acute form of skin inflammation, one can I think, without scruple, bring this form of dermatitis, by means of the elementary necrosis, quite well into correspondence with the chemotactic theory of inflammation. But when suppuration and lymphangitis are added to subcutaneous bruises

there must be infectious, if not always recognisable, causes ; in many the traumata may only provide a favourable soil for micro-organisms already dormant in the body ; all these cases do not come under this category. The finer histology of the acute *purely mechanically induced* dermatites is, as one sees, a still unsolved problem of great importance.

Still better than in the acute inflammations of this form, one sees in the chronic forms that mechanical force alone has no great tendency to produce inflammation. In opposition to the innumerable host of the chemically induced and infectious dermatites, we painfully collect a small series of indistinct affections of mechanical cause, which are quite distinct from the others: the inflamed corn, the ingrowing nail, the mechanical intertrigo and the bullous formation due to friction in healthy people, and in those persons particularly disposed to it (epidermidolysis bullosa). Every single one of these forms has first to prove itself, on thorough anatomical investigation, a dermatitis. In the corn and ingrowing nail we must naturally exclude accidental, readily-appearing infectious inflammations. But it cannot be denied that the corn in the one case or the edge in the other induce of themselves a tender swelling and redness, which immediately disappears on the removal of the pressure. The bullæ on the hands of unaccustomed workers, and on the feet of those on forced marches appear after slight temporary friction between the basal and middle horny layer and become filled with clear serum ; if one removes the cover of the bullæ there is apparent a somewhat moist, reddish horny layer. If the friction is severer and more prolonged, we have a loosening in the middle of the prickle layer or between that and the cutis, the exudation is more fibrinous, and there also takes place an active escape of leucocytes from the cutaneous vessels. If the blister is opened the erosion becomes covered with a purulent layer, but there is never prolonged suppuration. These superficial losses of substance always heal in two or three weeks without a scar.

If the combined action of epidermic parasites and other chemical irritants from without are difficult to exclude in these last affections, it is almost impossible to exclude them in these forms of intertrigo which are ascribed to the simple mechanical friction of the contact surfaces. We have to consider here not only the stagnating and decomposing secretions of certain localities, especially the anal, scrotal, and inguinal regions, but the whole, particularly luxuriant, epidermic flora. Squash preparations of intertriginous skin are always rich in various forms of bacteria, whose growth is probably not without reaction on the skin. In view of these factors, it is very difficult to maintain the action of simple friction. The epidermis is usually macerated and its upper layer raised in stretches. The actual exudation is difficult to separate from the secretions of the region or those running towards it.

As indefinite as are these affections, so interesting will be their exact, as yet almost absent histological investigation, in regard to the main question whether these are purely mechanical inflammations, and how they are to be explained.

2. Traumatic Inflammation due to Physical Causes.

To this belong not only the inflammations of the skin caused by higher degrees of heat, but also those dermatites caused by light and the influence of electricity. Sunburn and electric burn induce very similar appearances: redness and painful burning, œdema, marked desquamation and pigmentation. The accompanying action of heat is quite irrelevant to the development of these symptoms; the severest sunburns take place in the cold air on glaciers. Evidently it is those rays of the spectrum which induce the most severe chemical action, the blues and the violets, which, in abnormal concentration in healthy people, in ordinary strength in those particularly disposed, induce this "cold burning" of the skin. That this is not limited to a simple "scorching," *i.e.*, simple pigmentation, but induces true inflammation, sometimes with marked exudation, does not appear remarkable, if we adopt the chemotactic theory of inflammation, for the actinic rays here under consideration, even alone, induce chemical combinations and decompositions in animate and inanimate nature.

There do not appear as yet to have been any anatomical examinations of sun and electric burns. This want is partly supplied, especially in relation to the pigment which developes, by the histological observations on those diseases induced by the rays of the sun on particularly predisposed skins, as xeroderma pigmentosm and my "sailor's skin," to which reference may be made.

Burns.

Since Hebra adopted Boyer's division of burns of the skin into three grades, we have been accustomed, surgically and dermatologically, to regard burns from their three most striking results: first, redness of the skin; second, formation of bullæ; and third, the formation of scabs. It is thus usually tacitly assumed that only the third degree of eschar formation is accompanied by a true necrosis of the skin, and the fact that every form of burning induces a necrosis of a lesser degree is consequently overlooked. Erythema caloricum is accompanied by a distinct thickening of the superficial horny layers, and a similar process accompanies the formation of bullæ, which is mostly overlooked, as, in comparison with the fluid exudation in the epidermis, it does not strike the eye. In the above division weight is laid in the

first stage only on the inflammatory reaction of the skin, in the last on the primary necrosis, which, as the predominant symptom, attracts most attention.

It is evident that no traumatic dermatitis is so fitted as the burn to distinguish the results of the trauma from that of the inflammatory reaction of the skin. It is only necessary to vary artificially to any degree the manner of burning, and to examine the burnt parts immediately and at intervals after the effect. One will then find, for example, which changes of the burnt skin are already present before the secondary inflammation leads to the formation of bullæ, and a part of the obscurity which has surrounded the sudden late appearance of bullæ will be at all events lightened. Up to now only the bullæ have been thoroughly examined by Bisiadecki and Touton.

I therefore, some years ago, requested Dr Koulneff of St Petersburg to examine, experimentally, the effect of my "mikrobrenner," as with it the temperature and the form of the burn are so easily controlled. The researches were carried out on men and rabbits. As the results in both cases exactly correspond, I describe them both together.

With the mikrobrenner we induced punctiform or linear dry superficial burns, and it is important—as Touton also did—first to learn to recognise the action of dry heat, for, as is well known, moist heat (scalding with water, steam) at once complicates matters by the addition of the powerful swelling factor of hot water. But, on the other hand, there is with the micro-cautery a certain amount of *pressure* which, if unimportant and minimal in its form, is not to be under-estimated in its action; for it is partly due to it that the secondary appearances of serous inflammation are diminished, so that bullæ only exceptionally appear, if the burnt part is subsequently exposed to an artificial hyperæmia or soaking. But, owing to this, the simple *primary* action of the burn can nowhere be better observed.

With the mikrobrenner we made vertical stabs into and streaks along the skin. In all cases the application was as short as possible. In the tracks of the punctures the action on the cutis tissue, on the streaks that on the epithelium was best observed.

The most striking symptom in the puncture excised immediately is a marked *thickening of the collagenous bundles* round about. The swelling of the collagen affects a cylindrical area two or three times as thick as the track of the stab. It diminishes gradually outwards, but never so much as to make any difficulty in determining its limitation. The innermost sheath of this burnt zone again showed somewhat smaller bundles, as these passed into the *superficial charring* on the wall of the canal, which evidently restricted their swelling. The

bundles, three to six times their normal width, stain more readily, they take up hæmotoxylin, carmine, and generally those colours to which they are usually indifferent. There is not only a simple swelling from evaporating water but a coagulation of the collagen with increase of consistence. That was evident on all parts of the skin.

The elastic fibres inside the thickened burnt zone are pressed asunder without constricting the broad, collagenous bundles, as they do when the swelling is due to acid. They stained somewhat less readily than in the neighbourhood, were in many places swollen and not well defined. The blood vessels and coil glands in the zone were compressed and converted into solid cellular streaks. The hair follicles were, at least laterally compressed, or margined the burnt zone without having suffered any mechanical changes; they are evidently more resistent. Then we see, close on the innermost charred edge, large *irregular spaces* in the coagulated cylinder, due to the sudden development of steam.

At the level of the papillary body we find the papillæ likewise swollen, thickened, and spherical, and owing to that in the immediate neighbourhood of the track of the stab, loosened from the epithelium, in places completely separated.

The second striking change is a *distinct elevation* of the *horny layer* round the track, forming a vesicular ring around the opening. The prickle cells in relation to this are all drawn upwards and converted into long spindles, which project from the cutis like a tuft of hair, particularly on the inter-papillary areas, and sometimes reach the elevated horny layer, sometimes are torn from it, and project free into the cavity thus provided. These cavities contain no exudation but are empty. having evidently been simply filled at the moment of burning with steam. The horny layer arches over the thus excavated prickle layer and extends somewhat into the track where it has been drawn in the act of boring. Nevertheless the horny layer is evidently present in excess at some distance from the canal, as is seen by its folding. Where the epidermis is penetrated by the track there is, as in the cutis, a fine charred layer. But the prickle cells lying further out are —apart from their mechanical deformity—not changed; in particular, the nuclei are all well retained and stain well, although all transformed into small rods.

We see here that immediately, before there is any question of an exudation from the cutis into the epidermis, there is a transformation of the prickle layer resembling vesicle formation. It might be supposed that the steam developed from the parenchymatous juice of the prickle cells led to the formation of spaces and thus to the elevation of the horny layer. But if this was to be regarded as the only and primary force the formation of spaces would correspond to

the heat developed; and should be most marked immediately adjacent to, and slighter further from the track; while on the contrary—as already noted—the horny layer directly at the track is pressed in. Here comes into consideration a factor to which sufficient attention is not paid, the *expansion* of the *horny layer due to heat.* I drew attention to this and its significance in pathological processes in 1881 at the International Congress in London, after I had investigated experimentally this expansion both with moist and dry heat. It is well known that all horny substances, for example whale-bone, are converted by severe heat into a ductile condition in which they are plastic; after cooling they retain their form like sealing-wax or metal; the barber utilises this property in curling the hair. By loading fine long horny shavings with regulated weights and warming them in places I could determine that the condition of melting and burning, was preceded by another, in which the horny substance became half fluid and plastic, was greatly stretched by a light weight and that it retained this length after cooling. And it is equally easy to determine that the stretching which the horny substance undergoes with the much lower temperature of hot water (40-100°) and which is accompanied by a taking up of water and swelling, again disappears on cooling and evaporation; here the elasticity and internal structure of the horny substance is not lost.

When consequently the hot point enters the skin the horny layer rapidly expands and is—if the point is not red-hot—not penetrated, but taken like a scabbard, with it into the skin, it tears itself from the prickle layer, which has less power of expansion, after it has drawn the prickle cells into long spindles, and retains after the withdrawal of the needle its excessive lateral expansion. It is now easy for the simultaneously developed steam to fill up the tear, and so immediately after the withdrawal of the burner there is in many cases a bullous-like elevation. Where the distension by steam is absent (in dry skin), the expansion of the horny layer, which then rolls up, its partial separation and the spindle form of the nearest prickle cells is nevertheless present.

Thus much that is obscure in vesicle formation becomes comprehensible. After the application of dry heat (not red) the horny layer, so far as affected is already softened, inelastic, loosened here and there from the underlying prickle layer and thus prepared for the actual formation of bullæ, which sooner or later—and then rapidly and exactly limited to the affected surface—becomes manifest. In scalding with hot water (40-100°C.) on the contrary the horny layer, at first overstretched and here and there loosened from the prickle layer, remains for the most part elastic, again contracts and the local-

isation and intensity of the later bullous formation do not correspond exactly to the affected surface, but generally more to the intensity of the local inflammation than to the primitive loosening of the horny covering.

The fact that almost exactly the same appearances are produced on the skin of the corpse also shows that they are due to the primary burn alone, and are physical in their nature. Here also we get the solid swelling of the collagen in the neighbourhood of the stab, the steam spaces in it and the superficial charring of the surface in contact with it, then the overstretching and partial loosening of the horny layer and the bladder-like steam holes in the prickle layer and the spindle form of the adjacent prickle cells with retention of their nuclei. Only the swelling of the collagen is less in degree, which may be due to the more rapid cooling of the hot point in the skin of the corpse or to the rigor mortis.

The *streak* of the mikrobrenner presents itself on section as a semi-circular channel sinking into the cutis about twice the breadth of the epidermis. This is clothed with overstretched, folded or torn, rolled-up horny layer, charred above. On this follows the stretched semi-spherical prickle layer and the semi-spherically distended papillary body. The parts driven under the influence of heat into the upper layer of the cutis are—just as the collagen around the stab track—swollen, and are converted into a homogeneous mass, in which only a few excessively compressed nuclei are visible. Where the prickle layer is thick, this homogeneous burnt zone is composed of it alone; when thinner the change extends into the papillary body or with greater pressure of the mikrobrenner, even into the cutis. The blood vessels close under the depression are, by the swelling of the collagen, completely compressed and emptied of blood.* At the side of the burnt streak, the swelling and homogenisation of the prickle layer ceases almost abruptly, perfectly normal prickle cells margining the scab.

This change in the burning streak shows that a severe and more prolonged effect of heat has, on the uncornified epithelium, the same effect as on collagenous tissue; firm swelling, probably accompanied by coagulation. The lesser displacement of the horny layer in the streak has as its result that the epidermis is less torn; it shows no holes but is on thc contrary compressed by the slight pressure. A severer pressure employed during the action of heat welds both epidermis and superficial cutis into a dense homogeneous tissue.

So far the primary effects of dry heat. The secondary ones I will

* It was this experience which led me to give up the treatment of rosacea by scarifying, and to use only the mikrobrenner.

describe from experimental burns, especially from rabbits, which I have in every stage, from twenty-four hours up to the seventh day, that is, up to almost complete healing. After the first twenty-four hours—both in men and rabbits—the appearance of the streak itself is little altered. But the cutis for some distance round is somewhat swollen, all the blood-vessels, with the exception of those passing directly under the streak, are dilated, show marginal position of leucocytes and emigration following the direction of the scab. The connective tissue cells around the vessels are increased in size, and apparently also in number, and may be clearly distinguished from the multi-nuclear leucocytes escaped from the vessels. Around the homogeneous burnt zone leucocytes are collected, as yet only in moderate numbers. In the zone itself there are no leucocytes. Where hairs which share in the homogeneous swelling like the surrounding cutis are embedded in the burnt zone, the leucocytes accumulate outside the follicle, under the swollen area.

After two days the leucocytes in the neighbourhood of the homogeneous burnt zone have definitely increased in number. By entering the narrow spaces which remain on the external margin of the burnt zone between the swollen collagenous bundles, they form net-shaped figures, which consist of closely-pressed leucocytic nuclei, among which here and there can be distinguished persistent connective tissue nuclei. There now appear, in the neighbourhood of the streak, epithelial mitoses, and at the same time a fine edge of epithelium begins to make its way from the side between the uninjured cutis and nucleated external zone of the scab. The foremost epithelia show no mitoses; the epithelium does not advance, but is pushed on from behind.

The events of the next three days may be grouped as follows:—While the local leucocytosis and the dilatation of the vessels diminishes, the œdema of the cutis under the scab increases, the spaces between the collagenous bundles dilate, but contain relatively few leucocytes. These have ascended into the outer nucleated zone of the scab, but no more follow in the same quantity. In this zone they now form compact, thick, often radiating streaks. Beneath this nucleated zone the young epithelium closes, like an iris diaphragm, and is distinguished by the width of its lymph spaces. By its means the (in section) semilunar shaped scab is sequestrated and begins to loosen from the side; the inner homogeneous and the outer nucleated zone can still be distinguished. On some preparations where the leuco-serous inflammation has led, near the scab, to the elevation of the horny layer, and vesicle formation; these, as well as the underlying cutis, are free from leucocytes; only serum is here exuded, the leucocytes have only reached the outer zone of the scab. They evidently share with the young epithelium the function of separating the scab from the healthy tissue.

On the sixth and seventh days after the burn we have a slight, channel-formed, sunken, somewhat œdematous cutis, with completely regenerated epithelium, in which, however, the lymphatic spaces are of quite abnormal width, and where the keratinisation still takes place parakeratotically, without a granular layer. On this lies, almost com-completely loosened, the dried up and diminished scab, still distinguishable on staining, into two zones. In some preparations it is raised up by a marked inflammatory exudation consisting of serum and leucocytes, which, with the epithelial covering so œdematous, is evidently very easily induced, as clinical experience also teaches. It may further be noted that the elastic fibres in the œdematous skin have suffered very severely and only stain very faintly.

How does this minimal burn correspond to the grades named at the beginning? Taken strictly we have before us the third grade, a scab and its removal. But it is of minimal dimensions—clinically, a black crust like a streak of ink—and its elimination is dry, by epithelial undermining of the scab, not by suppuration and granulation, so that it is impossible that it can represent the highest degree of burning. Nor does this burning belong to the second degree, for it forms no blebs, evidently because the vessels lying directly under the scab are made bloodless by the method of burning, and thus all re-active inflammation is smothered. So we have—in spite of the scab—only the first degree before us, and indeed every clinician would, in regarding the minimal scab and the macroscopically erythematous spot, regard it only as the first degree of burn. The formation and removal of the scab as described is then, only in a somewhat severer and deeper extension, the same as the superficial callosity observed in other burns of the first degree. But we have not only learned more of the manner of the primary action of heat, we have also seen that the erythema of the first degree of burn is truly inflammatory and is accompanied by free exudation, after which an œdema of the cutis may for a long time remain. The inflammation is leuco-serous, and it would seem that the distribution of the leucocytosis is completely dependent on the scab, the leucocytes only collecting around it, and the serous exudation lasting longer than the emigration. The serous exudation also explains the œdematous condition of the epithelium, the parakeratosis and the scaling which usually follow burns of the first degree.

Bisiadecki found on the skin of human corpses in the smallest bullæ of burns: dilatation of the vessels, œdema of the cutis, swelling of the papillary body, and the formation of cavities in the prickle layer. The cavities were, as in small-pox, penetrated by long-drawn threads and spindles, some with, some without nuclei, which Bisiadecki refers to the prickle cells, while the exudation raises the horny layer

from the cutis. He draws attention to the inter-epithelial character of this cavity formation and the absence of cellular œdema.

Touton worked on quite different material—namely, on bullæ induced by hot sealing wax, on the paws of kittens. The very thick horny layer opposes a lasting resistance to the stream of exudation, therefore it acts more intensely on the prickle cells. Therefore, in contrast to Bisiadecki, Touton found a marked swelling of the latter with diminution of the staining activity of their nuclei, and further, "a very marked coagulation of the cell protoplasm with disappearance of the nucleus from the absorption of exudation fluid." In longer standing exudations the early induced, firm, granular, thready products of coagulation are again liquefied and converted into soft, granular, crumbly masses. The well-marked papillary body of the cat's paw leads to a septation of the bullæ, in that the epithelium, dipping into the inter-papillary furrows, is compressed to strings, and later forms sheaths for the chiefly supra-papillary areas of softening. The conclusion of the bulla formation after twenty-four hours is indicated by an emigration of leucocytes into the cavity, filled with serum and fibrin. Then begins the encapsulation by growth and cornification of the epithelium.

I have seven cases of bullous eruption after burns, four taken from the corpse, three excised from the living after intentional burning. Of the former two cases are old, and the details are unknown; of the others, one was from a child who died from a burn, and had on the scrotum a series of tensely filled bullæ the size of peas, the other was from an adult; here the bullæ were mostly from the side of the hand and extended to the back and on the vola. The last three were induced on the arm of an adult by dry heat (Paquelin). From this material I can confirm the results of Bisiadecki and Touton, and I add a few other facts which help to reconcile their apparently contradictory results.

And first I would deal with the case of bullæ on the scrotum, which seems to me to represent the simplest and most frequent form of bullæ. The section shows a large, one-chambered bulla, reaching semi-spherically above the skin and for the most part filled with coagulated serum. Its contents are divided by horizontal and oblique straight or twisted bands of fibrin into irregular, polygonal, mostly rhomboidal areas (Fig. 2). With the high power and a good fibrin stain one recognises that those bands taking the fibrin stain are sections of fibrinously coagulated surfaces, by which the successively deposited masses of exudation, of different thickness, are margined. On both sides of the bands there are assembled any amount of fine round granules of fibrin, which are more sparingly distributed in the remaining mass of the coagulated serum. There were no threads

of fibrin in the bulla. Here and there there is, between the exudation areas, a small area taking the fibrin stain and evidently consisting of coagulated epithelium. An unbroken layer of the same substance hangs from the under side of the horny layer which forms the cover of the bulla; this is the original prickle layer

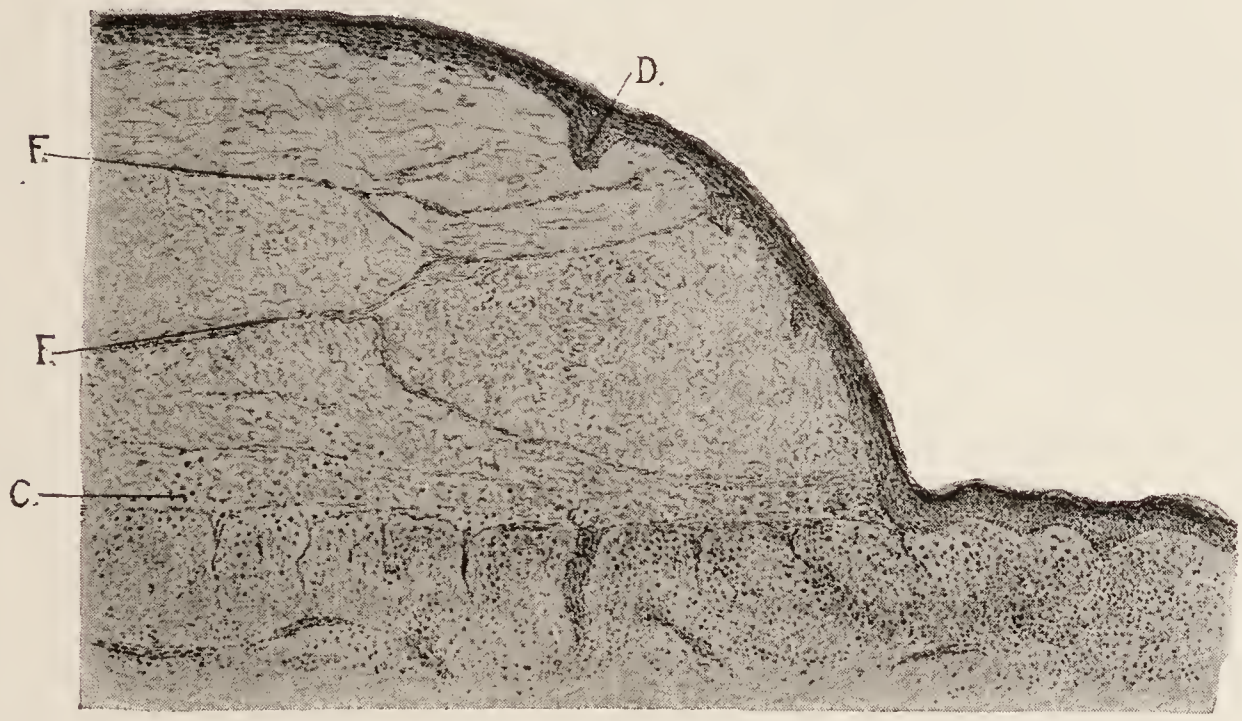

FIG. 2. Vesicle from Scrotum.
F. Fibrin Septa dividing areas of coagulated serum. *C.* Leucocytes.
D. Sweat duct, drawn from the corresponding opening beneath.

very much changed. The prickle cells are welded into a homogeneous mass presenting only remnants of nuclei, which shows, with fibrin staining, vertical, wavy, twisted dense threads—the persisting vertically stretched epithelial fibrillation; it is these which cause the fibrin colour of the whole mass. From this mass there extend tuft-like processes between the areas of serous exudation. And there project here and there from the base of the bulla, elongated and torn epithelial fragments, like tufts of hair. The rest of the base of the bulla is free from epithelium, the papillæ with rounded, swollen, flattened heads project naked into it and are covered by the deepest layer of coagulated serum, the only one which presents a few leucocytes. The cover of the bulla consists of the old overstretched horny layer, in which two layers can be definitely distinguished, an outer homogeneous one welded by the action of heat, which is partially raised up by numerous cracks from the normal inner one. At the side, the bulla is marked off from the healthy epithelium in different ways. In many bullæ the margin is quite sharp, as is particularly well shown by the methyl blue orcein stain. At a line vertical to the epidermis, the protoplasm of the prickle cells suddenly runs together, and instead of the methyl

blue, takes up the orcein. At the same time most of the nuclei of the prickle cells disappear and may be barely recognised as orcein coloured rods, while only a few very much compressed ones still retain the blue and are therefore very evident. The mass is now loosened from the swollen papillæ and passes directly into the mass under the cover of the bulla. At other parts of the margin there is a transitional zone between bulla and healthy skin, in which the epithelium is fissured and thus drawn out to long, sometimes torn spindles, as in the burn of the first degree at the side of the stab. Here also there is no exudation. But the epithelial spindles are mostly run together and coagulated. Is this a lateral overflow of the inflammation or a primary action of burning, only less than in the centre ?

To this question a few very small vesicles in the scrotum give the answer. These were due to the same burn, so that they are of the same age as the more developed bullæ and are only distinguished in degree. There are variously formed spaces present in the prickle layer ; the prickle cells are drawn out to vertical torn spindles, and run together into homogeneous, almost a-nuclear masses, which, with the above-mentioned stain, take the orcein. The orcein here reaches further outwards into the upper prickle layer than into the under, *i.e.*, the heat coagulation is more limited inwards than outwards, which, as the burning comes from without, is not surprising. In the spaces in the prickle layer there is no exudation, so that these are not due to exudation but to the steam developed in the act of burning, or to the friction and displacement of the over-stretched and loosened horny layer.

These minute, dry vesicles (sit venia verbo !) have just the same structure as many of the marginal parts of the large bullæ. Neither have anything to do with the inflammatory reaction of the skin or the accompanying exudation. They are due directly to the act of burning, and according to taste indicate less affected areas of the skin or burns of the first degree. But there is not only a loosening of the horny layer, but at the same time a widespread heat coagulation of the prickle layer, and everything is prepared for the rapid appearance of a bulla ; but, of course, instead of this we may have a throwing off of a dry epithelial scab, a scale.

And now we can definitely conclude that the dead, stretched, and torn prickle layer which hangs on the under side of the cover of the bulla has not coagulated and perished after its separation from the papillary body by the fluid of the bulla, but that this took place when it was elevated in the act of burning. Did we not know that the structure of this was exactly the same as that of the minute exudation-free areas, we would come to this conclusion on considering a second form of combustion bulla, to which I now turn, and of which the bullæ

on the side of the hand form a typical example. While these above described correspond to the results of Bisiadecki, the following agree with the contradictory ones of Touton.

In this form we have not simply to do with a complete primary destruction of the epidermis and its secondary elevation by sero-fibrinous exudation, but with a weaker primary action of heat with a gradual transition to an epithelial degeneration, caused by the inflammatory exudation. To Touton's cat's paw, the vola manus which I examined at least partly corresponded. But the resemblance is not due to this alone, for another of my cases with thin horny layer had the same appearance.

The bulla is here also simple, but contains only little free exudation, for most of the space is taken up by swollen and otherwise degenerated epithelium; in many places there are complete epithelial bridges between the cover and the base of the bulla. But there is no trace of any horizontal formation of layers of exudation of different age, there was rather here and there a sort of vertical division by compressed cords of epithelium, though there was never a complete separation of individual parts of the bulla, as in small-pox. The contents of the bulla rather resemble a curdled gelatinous mass, with a few firm threads and membranes. Where the formation of the bulla is simplest, one can recognise three layers. The lowest covers the papillæ, and fills the inter-papillary furrows, it consists of swollen epithelial cells, mostly separated from each other, and rounded or drawn out to the shape of clubs, which, with the methyl blue orcein method, partly retain the blue and partly take the orcein, while the nuclei retain the blue longer than the protoplasm. Many of these lumpy, loosely connected epithelial cells contain several (6-8-12) nuclei, which lie closely together in the middle, are of the same size, are facetted and must have arisen by amitotic division, for no mitosis is evident. We have therefore to do here with ballooning degeneration of the epithelial cells directly over the papillary body (*conf.* Varicella, Zoster, and Variola). Many of the ballooned epithelia are formed like pointed clubs, and pass into cord-like compressed epithelia running vertically through the cavity.

The intermediate division of the bulla is mostly filled up with a cellular debris, which, with the above method, takes up no methyl blue. The nuclei do not stain, the inner zone of the protoplasm is in most cells granularly degenerated; as in many is the ectoplasm, but there remain also many segments of the outer fibrillation of these cells which form together, and in combination with those already referred to as completely compressed thread and cord-like epithelia, an irregular net of firm consistence. Thus in this intermediate area there are no completely fluid contents.

Above, towards the cover of the bulla, the ectoplasm of the cells retain, more and more, their form and consistence, while the endoplasm is more purely liquefied, either in the form of a simple cavity (Leloir's altération cavitaire) or in the form of a fine reticulum with liquefied vacuoles (my "reticulating degeneration"). A pure intra-cellular mesh-work is present in many places (as in small-pox). Then follows the very broad granular layer, remarkably well preserved, and finally, as the cover of the bulla, the horny layer. So far as the thick horny layer of the palm reaches it is thrown into folds and partly separated into two layers.

If this description suited all parts of these combustion bullæ the matter would be pretty simple. Deep down we have the ballooning, nearer the surface the reticulating degeneration, in the middle a combination of both, and as a whole, changes very similar to those in the vesicles of zoster. But in other places we find modifications of this elementary type in two directions. There are places where neither of these forms of degeneration is regularly developed, where the degeneration first commences under the influence of the exudation. The deeper epithelia are then not completely rounded and separated from one another, the upper not completely reticularly degenerated. One has an epithelial mass of increasing reticular quality, but which presents no typical form of degeneration.

Then there are areas where the primary coagulation from heat was somewhat more developed, and where consequently none of the ordinary colliquative degenerations could typically form. Then there developes a pretty homogeneous epithelial debris, in which the subsequent exudation only forms a fine fibrinous net. There are also in the regularly degenerated parts here and there fragments of fibrinous nets, certainly more frequently than in the first described, more serous form of bulla.

The other bullæ which I have examined agree more or less with the one or the other extreme, and at the same time bridge over in many connections the sharper differences. One of the older bullæ corresponds exactly to the first described form, as do two of the artificially produced ones. In all, the epithelium is, as a whole, vertically stretched, coagulated in this position and elevated from the papillary body. The contents consist of more or less densely coagulated serum and little fibrin. In a bulla excised seven hours after the burn, a very delicate fibrinous net was present in the serum. In the older bullæ the fibrin formed coarser beams and membranes.

Another of my older bullæ shows, on the contrary, in addition to beautiful ballooning degeneration of the deeper epithelium, a large amount of free exudation in the centre of the bulla, with considerable

elevation of the horny covering, much fibrin, and a marked immigration of leucocytes. Both in the bullæ and in the cutis the leucocytes are surrounded by a fine fibrinous reticulum. One of the artificially induced bullæ supplied a contrast, for here the pretty well retained epithelium under the cover of the bulla and on its base, shows no stretching but the commencement of ballooning degeneration (swelling, multiplication of nuclei), and yet the cover is separated from the base by an abundant sero-fibrinous areated exudation.

I believe that we are now in a position to present a uniform conception of the burn bulla. *The tendency to bullous elevation of the epidermis is supplied* eo ipso *by every burn*, on the one hand, by the over-stretching of the horny layer by heat, and on the other, by the steam suddenly developed from the parenchymatous juice of the prickle layer and the lymph of its spaces. If the subsequent exudation does not lead to bullous formation, this is due either to the weakness of the exudation, to obstacles to exudation in the centre (as in the streak of a mikrobrenner), or a too severe primary necrosis. The first cases are burns of the first degree, as in them only an erythema is present, the latter of the third degree.

Those cases which are disposed to the formation of bullæ by the primary action of heat, and in which marked exudation follows, are of a different nature according as the primary necrosis affects mainly the horny layer and the prickle cells lying next it, or the whole prickle layer. In the former, the weaker burns of the second degree, the horny layer is only stretched, the prickle cells are not yet drawn out and torn asunder, and only partly show the commencement of heat coagulation. When the exudation sets in later, they undergo colliquative changes similar to those in the epithelium in many inflammations ; there is ballooning and reticulating degeneration with more or less tendency to form a structureless epithelial debris, if the exudation is not enough to elevate the horny covering, and thus acts long and severely on the prickle cells (cat's paw, Vola manus). Or the loosened horny layer gives way, and between the colliquatively changed (old burn bulla) or pretty well preserved (artificial bulla, twenty-four hours) prickle cells, a moderate sero-fibrinous exudation makes its way.

But when on the contrary the burning induces coagulation in the prickle layer, and the horny layer is at once elevated by the necessary development of steam, when the prickle layer is torn or separated from the cutis and vertically stretched, colliquative changes can no longer occur in the prickle cells ; they remain unchanged or coagulate still more firmly. But underneath them collects a profuse sero-fibrinous exudation (four of my cases). In severe burns of the second degree

almost the whole contents consist of a thin fluid serum with a little fibrin, while the firmer epithelial debris-like contents are found in the weaker burns of the second degree. In all cases the method of the later bullous development is measured by the degree and extent of the primary burn.

I have up to now passed over the changes in the cutis so as to consider them together, as they are the same in all burns of the second degree. The blood vessels of the papillary body and the cutis, and often of the hypoderm, are dilated, and so are the lymphatics. There is usually a considerable œdema of the papillary body and the upper half of the cutis. The papillæ are œdematous, globularly swollen, flattened, and often form an even surface. The collagenous tissue is loosened but not degenerated, but the elastic tissue in many places stains poorly, the fine fibres of the papillary body are mostly gone. Leucocytosis developes in different degree, but is usually insignificant. Usually there are only a few leucocytes on the under side of the bulla. A larger collection in the cutis and in the bulla gives evidence of secondary chemotactic action from pyogenic organisms, which are almost always found in long standing, untreated bullæ. The connective tissue cells are multiplied but not otherwise changed.

How then is this marked, sero-fibrinous inflammation of the skin to be regarded? One usually thinks of it as directly dependent on the act of burning, as a direct injury of vessels by heat, which in Cohnheim's sense might be the "cause of inflammation." But this would leave completely unexplained why the swelling and formation of bullæ do not begin immediately after the burn, but often very much later, and how, further, the changes of the skin are in all cases almost the same, while inside the actual burnt zone they present such differences. But, in the first place, all histological evidence that the burnt zone, in burns of the second degree, extends into the cutis is absent; at least, if we regard as necessary evidence, material changes in the constituents of the cutis (as above in burn stabs and streaks). A further extension of the burnt zone with invisible, simply molecular vascular changes I regard as an indiscussible hypothesis.

It all appears to me, on the contrary, very clear if we only locate the primary effect of the burn where we can see it—in this case in the epidermis—and regard the later inflammation, with its exudation and bullous formation, only as the result of the burning and the death of more or less of the epidermis. The inflammation would then be chemically induced, and the chemo-taxis of the products resulting from the burn would measure its degree.

Burns of the third degree have not yet been thoroughly examined histologically. Clinically they are grey, smoky or black, completely

charred, dry scabs, to which the burnt epidermis still adheres; or they are moist, brown or yellow, from which the epidermis is torn away, having adhered to the hot object or to the clothes. In deeper scalding with boiling water the surface is grey, swollen and dry, or whitish, transparent and moist, from bullous elevation of the epidermis.

The numerous pieces of skin which I have for histological examination came from a fatal widespread burn of unknown cause. The epidermis is everywhere elevated, the cutis has a honey-yellow transparent colour (like a sucking pig), but does not appear to be swollen; the panniculus is thin and whitish, and underneath it is the apparently normal muscle. The most striking phenomenon is the transparency of the cutis, through which the vessels, filled with coagulated blood, everywhere shine as plainly as in a skin injected and made transparent by carbolic acid or anilin oil. Microscopical examination shows that this transparent cutis consists of somewhat swollen collagenous bundles, lying closely together and compressing those vessels which are empty and the coil glands to small cords. The nuclei of these last, as well as those of the rest of the cutis, stain well; but are diminished in size and rod-shaped.

The elastic fibres are compressed and stretched between the somewhat swollen collagenous bundles, but are otherwise well preserved. The cavities of the fat cells contain no fat, as is always the case in alcohol preparations, but retain their ordinary round form, an indication that the fat was not melted by the burning.

I had next to find out whether these changes were primary, and induced by the act of burning alone, or whether secondary changes had played a rôle. I therefore took a larger series of burns on the normal skin of men and pigs, and compared the burnt pieces with unburnt. The former, sometimes with, sometimes without the panniculus, were heated dry in a test tube or directly in the flame until the edges were charred, or were heated quickly with water to boiling point; they gave the following results.

The skin was always yellower, more transparent on section and swollen in its thick diameter. But while, with dry heat, the skin was much diminished in surface area, in boiling water that also was increased; in this case, then, the increase was in all dimensions and the skin was still more transparent and gelatinous. It is well known that the cutis is converted into gelatin by prolonged boiling, and the rapid gelatinous swelling in boiling water is the first step in this direction.

Where the cutis was previously distended with blood, the vessels, after dry combustion, shine through as brown coagulated cords. Where charring has taken place at the edge, a thin layer of the cutis

is coloured black brown, and immediately beneath, torn and distended by a quantity of steam bubbles; so that a whitish yellow, irregular zone follows on the black edge. The fat of the panniculus is liquefied by dry heat and partly sucked up into the dried cutis; with boiling water the fat is of course also liquefied, but is so well enclosed by the coagulated collagenous tissue of the panniculus that it never escapes. The collagenous tissue, perhaps from its great richness in blood vessels, appears here to diminish, the fat lobules are very prominent in boiling water. The horny layer under the charred margin is mostly thrown into folds and often considerably elevated by white steam bubbles. Its increase in surface and thickness are still more noticeable on boiling, which usually immediately leads to the solution of the horny layer.

We see therefore that the cutis becomes more transparent in all cases from heat, and it is very likely that external dry heat produces a formation of steam in the cutis, as is indicated by the steam bubbles, so that there is actually a commencement of gelatine formation. From the transparent appearance of the cutis alone we can draw no conclusions as to the nature of the burn. For simple drying, after removal of the epidermis, can make the cutis horny and transparent.

But a careful microscopical examination enables us to draw more definite conclusions. On the dry heated (burned) pieces of skin the collagenous fibres have definitely increased in thickness and compressed all the elements between them; the empty vessels, the coil glands, and even the hair follicles. They retain all stains, basic as well as acid, better than normal, which may be ascribed to the removal of water or to coagulation. The protoplasm of the enclosed cells is no longer recognisable, but the nuclei still stain very well; they are deformed into rods and irregularly indented, often as if nibbled. The elastin and the granules of the mast cells show quite peculiar changes. The elastic tissue as such has in all cases completely disappeared, but the places where it was have taken the elastin stain (acid orcein). The elastic fibres are also melted by the dry heat and the substance which retains the colour covers or imbibes the adjacent collagenous, otherwise unstained, bundles. That this is so, one can recognise on the less heated part, where the remains of the elastic fibres run into broad plates and nets. A similar transformation affects the granules of the mast cells. In place of the beautiful and regularly red granular cells (polychromic methyl blue) we find rosy red patches in which, in addition to the nuclei, a few irregularly formed, dark red, different-sized granules are seen. Often by the running together of these red halos all the enclosed parts, particularly hair follicles and blood vessels, are

surrounded by complete red borders. In many places the collagenous bundles are separated by round holes (steam holes). The extent of the horny layer is always increased by dry heat and it is often welded into a homogeneous layer. The prickle layer runs together to a homogeneous mass with closely packed nuclei but no recognisable cells. The nuclei mostly assume a palisade form, *i.e.* they are stretched between horny layer and cutis, without actually being drawn out into spindles. As this compression of the nuclei cannot take place if the papillary body is equally stretched with the horny layer, it must either retain its form or shrink. It seems to me that the latter is the case, and as if we had a lateral shrinking of the connective tissue as of the rest of the cutis. If the horny layer is particularly thick, as on the sole of the foot, steam bubbles develope inside the prickle layer, whose walls are formed of cells, blended but not drawn into spindles. The fat of the panniculus has disappeared and the fat cells have collapsed.

The results of the action of boiling water are similar, but still they differ in many particulars. There is much more marked swelling of the collagenous bundles, which appear perfectly homogeneous and abnormally twisted. The elastic fibres have here also disappeared but without having passed on their elastic substance to the neighbouring collagen; on the contrary, we often find here swollen, but still well-preserved twisted threads. The nuclei stain as well as in dry heat, but are more regularly round or oval. The mast cells also are rather better preserved, although here and there we meet with the transformation into diffuse coloured halos with a few large granules.

The horny layer is much more increased in surface and thickness, and the individual horny cells stand out as in a honey-comb; there is never any welding into a homogeneous layer. The prickle layer also shows characteristic differences, in that the cells are stretched like spindles between horny layer and cutis, they are often torn and present the well-known hair-tuft-like appearances on the base and covering of the bulla. There is no punctiform bursting of the cutis by steam bubbles, or collapse of the fat cells.

These details supply not unimportant data for the forensic differentiation of the varieties of burns of the skin. If we enquire how the above-described appearances from the corpse are to be explained, we can say with certainty that neither dry nor moist heat had acted sufficiently long on the skin to burn the cutis itself. For then the elastic tissue must have disappeared, while we find it well preserved. The heat can only have acted on the epidermis, and led to bullous elevation, whereupon the cutis, laid bare and heated, rapidly became completely dried, and thus horny and transparent.

Histologically we have to distinguish three stages of burns of the third degree. In the slightest cases only the epidermis is burned and raised in blisters (burn of the second degree), but, through further action of the heat and diminished protection, the skin dries up to a rind, which eventually undergoes necrosis and exfoliation (the above case). Where the action is deeper we get the changes described of the constituents of the skin as preceding charring (in dry heat). Finally (in dry heat) there comes the charring itself, a very rare event in the living, which can only occur when the patient is unconscious (*e.g.*, epileptics). The precedence of a whitish steam bubble zone to the charring is a purely physical phenomenon and is developed as well in the dead as in the living skin.

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3. Traumatic Inflammations from Chemical Causes.

All three kingdoms of nature supply the irritants which chemically induce inflammations of the skin, and their number and multiformity is almost inexhaustible. The further our knowledge of strange people and lands extends, the more complicated and numerous become our branches of industry, we become acquainted with new injurious factors, which accidentally, or in working with them produce inflammation on the human skin. But certainly all the lesions ensuing in this way are not to be reckoned to the inflammations, and we will here at once separate some groups which, although related to the here-described chemically-induced inflammation, still do not belong to it. These are chiefly four groups.

First of these are pure *urticarial* dermatoses which are caused by nettles, sea-anemones, the sting and bite of many insects and caterpillars' hairs. These we have already considered with the disturbances of circulation. Certainly there are here mixed forms of spastic œdema and true inflammation in which, after the departure of the vascular cramp, an inflammatory nodule remains; still these are relatively rare.

Then come *hyperkeratosis* with *closure of the follicles* and *comedo formation* which develope under the chemical action of tar and paraffin, in workers with them. These sometimes go on to the formation of follicular horny cysts.

Further, we cannot regard as inflammation the *simple superficial necroses*, which are caused by the weaker caustics, nitrate of silver, chloride of zinc, and the large class of phenols (carbolic acid, resorcin,

salicylic acid). These appear, at least chiefly, to exert only a negative chemotactic influence on the tissue. They result in drying of the tissue, scab or scale formation, and heal without inflammation after throwing off of the necrotic area.

Finally, no inflammation follows on many, perhaps most of the *deeper caustics*, concentrated acids and alkalis, if the addition of secondary causes of inflammation, particularly micro-organisms, is prevented. The appearances on the skin are those of simple necrosis, ulceration, and granulation.

After the removal of these groups there still remain many diseased appearances which we must reckon to the inflammations, and it is only to be regretted that our histological knowledge does not come up to our clinical. It is certainly to be hoped that this gap will be filled up before long, as no other chapter is so accessible to experimental work, and scarcely any other so fruitful in promise for the widening of our pathological views.

There was a time—which is represented in the text-book of the older Hebra—when one recognised in the eruptions provoked by chemical irritants representations of the daily familiar chronic eruptions. While a closer clinical observation had already found sufficient grounds for regarding this view as mainly wrong, histology provided the first series of incontrovertible proofs of the difference between acute dermatitis and those eczematous, impetiginous and bullous skin diseases; further proofs we will obtain in the investigation of the causes of these last.

We can hardly hope to succeed in finding for all types of inflammatory skin diseases, artificial inflammations caused by chemical traumata, which might serve as prototypes. It is more important that, as is found in the infectious inflammations of the skin, every separate, etiologically different affection appears different histologically, and—pathologically considered—is an entity. But with this reservation, and for greater convenience, the phenomena may be arranged into larger groups.

I separate the chemically induced inflammations of the skin into two main classes—I. *simple*, and II. *complicated* inflammations.

Under the simple inflammations we have three very different groups—1. *erythema*, 2. *vesication*, and 3. *the formation of follicular papules.*

Iodine inflammation may serve as the prototype of the simple erythema, which almost always runs its course without the formation of vesicles; a formation of vesicles alone without other appearances of inflammation is caused by cantharidine and chloral in concentration, the vapour of tar oils and paraffin leads to the formation of inflamma-

tory papules, which are located in the follicles. It is, of course, evident that I can only name certain irritants, namely, the most familiar for each form of inflammation, and that, on the other hand, only the most characteristic effect of the irritant can be used for the grouping of the eruption. Thus it is familiar that by the excessive action of iodine, necrosis can be induced, by a weak action of cantharidin, an erythema. It may appear doubtful whether the inflammation of the tar and paraffin papules is to be ascribed alone to the chemical irritant, or whether organisms come into play (as in acne) which only, under the influence of hyperkeratosis and the more complete closure of the follicle, induce inflammatory irritation.

In the second division of *complicated inflammations of chemical origin* we have six groups.

1. Erythema + Œdema, caused by Chrysarobin, more rarely by Resorcin, Pyrogallol, Iodoform, and further by the stings of wasps, bees, and scorpions.

2. Erythema + Vesication (Eczema-like dermatitis) by Turpentine, Daphne mezereum, Arnica, more rarely by Chloroform, Sublimate, Sulphur.

3. Erythema + Folliculitis (acne-like dermatitis) from diluted Phenols, Mercury.

4. Erythema + Œdema + Vesication (Erysipelas-like dermatitis) from Rhus toxicodendron, Rhus venenata; more rarely from Iodoform.

5. Erythema + Papules + Pustules (Impetigo-like dermatitis) from Croton oil, Euphorbiaciæ.

6. Erythema + Papules + Pustules + Necrosis (Ecthyma-like dermatitis) from Arsenic, Tartarus stibiatus, Chromic acid and Chromates.

Iodine dermatitis.

We have already before us two thorough works on the inflammatory changes of the skin, after the external application of iodine, by Schede and Coën. The first carried on his investigations on the ears of rabbits, wherefore I can only give a very brief resumé. After painting with tincture of iodine there appeared first hyperæmia, then a marked œdema, which after twenty-four hours has again disappeared. Two hours after the application there commenced an emigration of leucocytes, which in two hours more closely surrounded all the capillaries and veins. After twenty-four hours the collection of wandering cells is so dense that one cannot distinguish the appearance from that of profuse suppuration, although it never reaches suppuration. Schede noted on the leucocytes, progressive changes from swelling of the protoplasm and luxuriant division of the nuclei, which, after the

rapid disappearance of nuclei and peculiar changes in the form of the protoplasm, conclude with their transformation into fixed connective tissue cells, while the old stationary connective tissue cells, like the collagenous tissue, show no changes. The unorganised leucocytes wander back into the lymph tracks, and after five days there begins a fatty degeneration of the old, and later also of the new formed cells, which after two weeks is not concluded, and probably by the degeneration of still more recently formed cells, lasts a considerable time.

Coën worked with the skin of men, rabbits, and guinea pigs, and devoted special attention to the formation of mitosis and regeneration. He found in all cases, after painting with tincture of iodine, an acute inflammation, which ran its course in about two weeks with the formation of new fibrous tissue. The material from men was got from painting parts which were to be amputated, a few days, and shortly before operation. After twenty-four hours there was marked emigration of leucocytes which usually showed several, very rarely only one nucleus. At the same time an exudation enclosing a net-work of fibrin is present in the lymph spaces. Leucocytes and exudation continue to increase the next day ; then the latter is absorbed, the fibrin undergoes fatty degeneration and the mono-nucleated leucocytes gradually outnumber the multi-nuclear. Within twenty-four hours mitoses are found in the endothelium of the blood vessels. They are likewise met with early in the prickle layer, the hair follicles, the sweat and sebaceous glands, and in the neighbourhood of vesicles which, in very free painting with iodine, are produced by vacuolisation and colliquation (reticular degeneration) of the prickle cells. The horny layer separates after repeated paintings. The changes in the connective tissue are on the contrary at first very slight—with the exception of the exudation—and are limited to scattered endothelial mitosis and a slight increase of mast cells.

On the animals (rabbits) where Coën could study the progressive changes through a longer time they continued to increase up to the ninth day. Then the mitosis disappeared and there was present a number of young connective tissue cells whose formation the author would attribute not only to the account of the endothelium and the fixed cells of the collagenous tissue, but also, at least in part, to the mono-nucleated leucocytes. Coën does not refer to a marked fatty degeneration of the old and young cells, only where the exudation is absorbing did he find fatty and albuminoid granules.

The material which I possess of iodine dermatitis consists partly of rabbit skin which was subjected to iodine painting by Dr Engmann in my laboratory, and partly of human skin. This latter was got from

the walls of indolent ulcers, which were painted with iodine at varying times before their removal, partly from otherwise normal pieces of skin from the corpse, painted with iodine while alive, which were kindly presented to me by Dr Glaser. According to my preparations one has to distinguish an acute iodine dermatitis from a somewhat different chronic one. The latter appears either as the after result of a simple energetic application of iodine, after the acute appearances have disappeared, or we meet it alone and more highly developed where caused by a series of rapidly following weaker applications of iodine.

In the acute iodine dermatitis the upper part of the prickle layer is, through the direct application of iodine and according to its strength, in greater or less breadth destroyed. The protoplasm of all the epithelia has run together and stiffened to a homogeneous layer in which only faintly stained nuclei are regularly distributed. This layer with the orcein methyl blue stain takes no methyl blue but only orcein. Immediately beneath, cut off exactly in line, follows the uncauterised healthy prickle layer, whose cells are increased and stain well. Here and there it is permeated by leucocytes. On the border between the scab and the healthy prickle layer leucocytes are assembled in greater quantity, and form, here in the middle of the prickle layer with the help of a small quantity of serum, a series of small vesicles, particularly above the papillæ. These vesicles develope solely through pushing aside of the epithelium, not through necrosis and colliquation, and their deep position inside the prickle layer is evidently the result of the deep-reaching cauterisation and coagulation of the epithelium, into which the leucocytes could not enter. While here on the border of the scab the leucocytes are numerous, they are only sparingly present in the papillary body and other parts of the cutis. But one can still recognise the dilated vessels from which they are still emigrating. Except for a slight œdema of the papillary body and an increase of the perithelia, there is nothing abnormal.

On the pieces of the same iodine skin, removed one to three days later, the primary scab with its contents of leucocytes is raised up by newly cornified epithelium and converted into a scale or a crust. The acute leucocytosis has completely ended, and the cutis is no longer œdematous. But the vessels are still dilated, and the increase of the perithelia has spread to the other scattered connective tissue cells of the cutis. These preparations form the transition to the pure chronic form of iodine dermatitis, in which, with the exception of a scale formation on the surface, no epithelial change and no leucocytosis is present. The skin appears altogether somewhat sodden, the blood-vessels are considerably dilated, and all the connective tissue cells, both the perivascular and the interfasicular, are strikingly increased, and form

an almost continuous net work in the skin. But they retain their spindle form. The skin chronically inflamed by iodine seems to me to be a very suitable place for studying the development of spindle cells into fibrous tissue.

A good protoplasm stain shows that the cellular elements of the skin, in particular all the epithelial appendages, are not only richer in granular and spongy protoplasm, but also have around them granular deeply-staining albuminous fragments. The lymph spaces of the epidermis are almost filled with these, as are those of the somewhat œdematous papillary body, and still more the immediate neighbourhood of the coil glands and hair follicles. In the fatty tissue there is a marked atrophy of the fat, while the cells, losing their fat, on the other hand store up granular protoplasm and swell up. The fat lobules then form—in their collapsed condition—loose, spongy, cellular areas with large net-like anastomosing spindle cells, many fragments of detached protoplasm, and very large lymph spaces.

A fibrin staining shows, on the other hand, that the under part of the cutis and the atrophic œdematous fatty tissue contains, not only granules of albumen, but large quantities of thready fibrin. This fills the deep lymph vessels with a thick, knotted mesh-work, the lymph spaces with a finer one, and the fibrin threads extend into the collagenous bundles, some of which are completely permeated by fibrin. In the superficial parts of the cutis the quantity of fibrin is much less, and we see from this, as from the general spread of the process, that the external application of iodine acts deeply, as is not surprising, considering the great volatility of iodine. Such a marked formation of fibrin in the tissue as in the chronic iodine dermatitis I have not found in the acute, but in this form also the lymph vessels contain thick fibrin tendrils; a tendency to the formation of fibrin is here also present.

So far as I can control Coën's observations on mitotic formation with the not very appropriate method of alcohol hardening and methyl blue stain, I can confirm, that, with the disappearance of the primary leucocytosis in acute iodine dermatitis, the mitotic formation in the epithelium increases. This leads to the replacement of the cauterised epidermis. I could find no mitosis in the cutis in chronic iodine dermatitis, but this I would ascribe to the method, for I found plenty of multi-nuclear spindle cells and endothelia. At least I believe that it must be concluded from my preparations that the cauterisation with iodine induces a still stronger nutritive influence on the protoplasm than it does on the mitotic formation and proliferation of the cells.

If we make a short resumé of these results the immediate acute action of the application of iodine consists in a cauterization of the

horny layer and on increased application of a part of the prickle layer, with resultant, rapidly transient, local leucocytosis, which never goes on to the formation of pustules. It is accompanied by transient dilatation of the vessels and œdema. After the exfoliation of the leucocyte-containing epidermic layers, there still remains a tendency to formation of mitosis and hyperplasia of the cell substance.

If a chronic dermatitis is induced by repeated weaker applications of iodine, it is characterised by a deeply extending general hypertrophy of the spindle cells, atrophy of the fat in the hypertrophying fat cells, profuse separation of fragments of protoplasm in the dilated lymph spaces and general slight œdema of the skin with separation of fibrin, particularly in the lower half of the cutis and in the hypoderm. A transition of the leucocytes into connective tissue cells in the sense of Schede and Coën I have not observed.

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Cantharidin-Dermatitis.

It is more than ten years since I—and shortly afterwards Touton—worked on the bullous formation following the application of cantharidin, and the subject has recently been very thoroughly and carefully investigated by Kulisch in my laboratory. He induced bullæ in considerable number on men and on certain animals (dog, cat, rabbit, guinea pig), and found characteristic differences in the reaction of different animals to the poison, both in the ease with which bullæ were induced, and in the finer histological changes. In general, however, there was over all a tendency to the formation of serous vesicles on a hardly reddened skin. From preparations which I controlled, and his account of them, I present the following description of the development of bullæ in man.

The human skin presents great individual differences in its sensitiveness to cantharadin; according to Kulisch's experiments bullæ developed with the same dose in times varying from one and a half to seven hours. They commence in the upper layer of the prickle layer with the development of small irregularly-formed cavities, which are filled with serum, cell debris and fragments of chromatin, and probably result from the breaking up of epithelia, as in the cutis beneath these places the signs of marked exudation are still absent.

One finds mitosis very early in the germinal layer, the upper prickle layer, and if the development of bullæ is long delayed also in the papillary body.

The formation of vesicles follows proportionately rapidly and violently, in that not only the primary small holes successively increase, but that they form the starting-point of a wide-spread elevation of the horny layer, which is accompanied by an irregular tearing of the prickle layer. Larger clumps of unchanged prickle cells always adhere to them and also to the base of the bullous space, while on other parts the horny layer alone forms the covering and the naked cutis the base of the bulla.

The contents consist at first of clear serum, to which later, when the epithelia in the blister fluid have degenerated, fibrin in greater, and leucocytes in much smaller proportion are added. The chief change is in those prickle cells of the upper layer which are raised up with the cover of the blister. They lose their prickles, their protoplasm becomes homogeneous and glassy, takes stains less well, and is finally entirely dissolved; somewhat later the staining power of the nuclear chromatin also suffers. The a-nuclear fragments thus formed, form themselves, clinging together under the pressure of exudation, into band-like, flat structures which further may again break down into granules. This secondary degeneration of the dislocated epithelium finally leads, like the primary, to the development of crumbling masses of albumen.

Rather remarkably, continuous proliferative changes accompany these degenerations. Both in the elevated cell complex of the cover of the blister and on its base, we find a few mitosis and further, cells in whose nuclei the chromatin is increased, and finally others in which certain loops of irregular but increased chromatin granules indicate the commencement of the pathological breaking down of mitosis.

Some hours after the elevation of the blister the fibrinous precipitate increases, and there now begins an immigration of leucocytes evidently not due to the influence of the poison, but induced by the poison of the degenerated epithelia. They are found mostly distributed in and between the most markedly changed epithelium of the cover of the blister, in the form of bands, horse-shoes, or sausage-like conglomerations. The leucocytes by no means increase in quantity proportionately to the greater age of the blister; they depend rather on the fibrin which precipitates itself in long existing bullæ in finely granular layers in the cavity.

Slow but considerable changes have all this time been going on in the cutis. At the beginning of the formation of the blister hardly any change can be recognised histologically. But later the lymph spaces and blood vessels are distinctly dilated, the former being surrounded

by enlarged connective tissue cells, and the elastic fibres of the papillary body here and there degenerated to fragmented masses.

The skin changes in the more chronic action of weaker cantharidin are somewhat different. There the proliferative changes of the epithelium are much more prominent than the more active appearances of sero-taxis. We find in the œdematous prickle layer, which is partly loosened from the cutis, in addition to ballooned epithelial cells, numerous ones with pathological mitosis, whose chromatin loops embedded in homogenised, swollen protoplasm may be partially broken down but otherwise well preserved, or others where the protoplasm is completely swollen, and which, therefore, appear pressed into a corner in a roomy space. The œdematous changes in the cutis are, in these cases, more pronounced, and the number of plasma and mast cells distinctly greater.

There are three things in particular which mark the cantharidin dermatitis. First, the fact that the poison exercises an unknown, directly necrosing influence on the protoplasm of the prickle cells; for it softens and degenerates at a time when the dilatation of the vessels and the exudation are still very slight and not recognisable histologically. But, along with this deleterious influence on the protoplasm, there is a second, favouring the formation of mitosis; along with the primary retrogressive, we see primary progressive appearances. The peculiar amalgamation of two so different phenomena leads to the pathological mitosis in which the beginning of the formation of threads is destroyed by the degeneration of the protoplasm.*

The third peculiarity of cantharidin is that it induces an almost pure serotaxis, which only gradually passes into a sero-fibrino-taxis. The later addition of leucocytosis is always subordinate, it is connected with the dying epithelium and never has the character of suppuration (in cats and guinea pigs it is almost entirely absent).

In hairless African dogs, which, in regard to the action of cantharides, most nearly resemble man, Kulisch, in addition to the histological symptoms described, was able to recognise a parakeratosis of the epidermis and a not insignificant attraction of pigment. These points must be attended to in future examination of human (pigmented) skin.

From this description of cantharidin dermatitis we have the satisfactory result that it presents quite a different process to that of eczema, and I might content myself with indicating the comparison of the two chapters. But as again and again, in the last thirty years, the analogy established by F. Hebra between eczema and the vesicular dermatites has been adopted without further proof and regarded as proved, it is perhaps not superfluous to indicate definitely the main differences here

* A similar paradoxical appearance is met with in tuberculin, where the poison also acts differently on protoplasm and nuclei.

and in the croton dermatitis. If one wishes to compare cantharidin dermatitis with the so multiform process of eczema, it can only be, so far as I see, through two comparisons of the undistributed middle. One may compare the cantharidin blister to one of the two vesicular eczemas or the chronic action of cantharides to chronic eczema. Now of the eczema vesicles the primary acute one, which appears on healthy skin and is therefore the only one which can chemically be compared to the cantharidin vesicle, is as different as possible from it. For it contains, in addition to serum, many leucocytes and no cell debris or fragments of chromatin, and is formed, not by the rupture of a considerable area of the prickle layer, but by the displacement downwards of the prickle layer from a point of the horny layer; it shows no primary epithelial necrosis, but only a secondary epithelial softening, no primary tendency to the formation of mitosis, and no pathological mitosis.

But if one will still compare the vesicle of chronic eczema with the cantharidin blister, he must first of all ignore that the first is formed on already eczematous epidermis, and therefore possesses quite peculiar qualities of basis, which the cantharidin blister does not. It is true that the exudation in both cases is first purely serous and later often serofibrinous, but the vesicle of chronic eczema developes from the punctiform exaggeration of the spongy condition of the upper part of the prickle layer, with simple compression downwards of the prickle layer from the horny; the cantharidin blister through the sudden irregular tearing of a, till then, healthy prickle layer. In spite of the pathological history of the eczema vesicle, there are absent here the direct epithelial necrosis, cell and nuclear crumbling and the pathological mitoses, which distinguish the cantharidin blister, and the mitoses are seated, not in immediate relation to the action of the poison but further away, in the surroundings of the vesicle.

The acute severe action of cantharides on the epithelium is one leading directly to necrosis of the protoplasm and to mitosis of the nuclear chromatin, while that poison which causes eczematous vesicles does not directly injure the epithelium nor recognisably favour the formation of mitosis, but acts secondarily and indirectly through attracting an exudation and separating a part of the epidermis.

The conditions in the cutis are also different; but I think I need not refer to their explanation nor to the main difference in regard to the presence of bacteria.

One is as little likely to confuse a cantharidin blister, carefully examined, clinically with an eczema vesicle, as histologically.

Things are just the same in regard to a parallel between chronic cantharidin dermatitis and chronic eczema, and it is only necessary in this connection to refer to the anomalies of cornification accompanying

eczema, the spongy condition of the prickle layer, the marked dilatation of the vessels, the œdema and the marked cellular infiltration of the cutis. The mitotic formation in chronic cantharidin dermatitis never leads to those progressive changes of the epithelial ridge net seen in chronic eczema.

Croton dermatitis.

The dermatitis induced by croton oil is distinguished clinically from many artificially-induced inflammations of the skin through two circumstances; the principal and primary affection of the follicle and the rapid formation of pustules at the mouths of the follicles. Very soon after the application there developes itching, burning, and redness; after a few hours the inflamed follicles raise themselves like goose skin over the surface. On the next day the perifollicular pustules are already fully developed. They heal without a scar. Repeated application may cause suppuration of the follicles, necrosis and formation of scars, but these are never so wide-spread as after the application of Tartarus stibiatus.

Kulisch also examined, in my laboratory, croton inflammation of the skin of men and different animals, of which the guinea pig and the hairless African dog reacted in a way very similar to man, while the ensuing suppuration in cats and rabbits was more diffuse and superficial. The macroscopically visible papule in man, corresponds always to the swelling of the surroundings of a lanugo hair and its sebaceous gland. The epithelium is little changed, the connective tissue cells of the hair follicle and its immediate neighbourhood are distinctly increased in number, and these peri-follicular, cellular infiltrations consist of small spindle cells with large nuclei; neither mast cells nor plasma cells are increased in number. At the same time there begins an emigration of leucocytes into the region of the follicular neck; and some penetrate the epithelium of the hair follicle. As this leucocytosis increases, the papule becomes a pustule which, concentrically surrounding the hair, occupies the upper part of the follicular neck. Then ensues from the vaulting of the horny layer covering the follicle, and downward pressure on the prickle layer, a true supra-follicular, and on further spread, an endo-follicular impetigo. Leucocytes are found in the further surroundings, infiltrating the epidermis, but the mouth of the follicle forms their centre of attraction. Up to now there are no changes in the epidermis other than those mechanically produced by the leucocytes; in particular there is no colliquative epithelial degeneration. In this and in the absence of early mitotic formation the croton pustule differs from the cantharidin vesicle; but of course mainly in the purulent character of the inflammation.

It is out of the question to compare croton dermatitis with eczema; it is still more unlike it than cantharidin inflammation. If one must compare it to an infectious inflammation of the skin, it can only be to purulent impetigo; but in the croton pustule no cocci are found.

The prominent rôle which the follicles play in the dermatitis makes it very probable that the oil, when rubbed on, preferably enters the follicles and sebaceous glands.

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Supplement.

In concluding the consideration of the dermatites caused by chemical irritants acting externally, we must consider certain inflammations of the skin which are the result of the circulation in the blood of definite chemical substances. Such lesions of the skin may be produced by drugs such as iodine and bromine, or through injurious products of tissue change, such as sugar (diabetes). These have a peculiar histo-pathological interest, and some have already been histologically investigated. But the processes by no means always cause inflammation of the skin, but much oftener (see drug eruptions) vasomotor disturbances, erythema, erythanthema, hæmorrhage, or regressive metamorphoses (gangrene). Such a simple and uniform characteristic as that of the dermatoses, caused by external application of chemical substances, is not possible in the very polymorphous and individually different diseases of the skin, caused by internal administration of iodine alone. This is due partly to the importance of the "personal factor" in their development, partly to the circumstance that these dermatoses are by no means all induced directly by the chemical bodies, but perhaps first by their combination products in the tissues, and probably many, only on the addition of a third factor, namely, micro-organisms. I prefer, therefore, to give to the whole group of varying appearances, which are due to the *internal* administration of such bodies, an unprejudiced common name, such as iododerma, bromoderma, meaning by that, that the skin is under the influence of the circulating iodine or bromine. A descriptive adjective, *e.g.*, Iododerma pustulosum, bullosum, acneiforme, or pemphigoides, indicates sufficiently both the form and the method of development of the dermatoses. This method of indication, adapted to all languages, recommends itself

as possessing an *immediately comprehensible contrast to the lesions due to external application,* which, from their much clearer and simpler pathological action, we indicate anatomo-pathologically, *e.g.*, iododermatitis, carbolic gangrene, tar comedones.

The so-called "iodine acne" and "bromine acne" are excellent examples of these inflammations of the skin, and their description may represent provisionally the whole most interesting class, which well deserves systematic experimental investigation. Diabetic dermatosis will be found under the regressive disturbances of nutrition.

Iododerma pustulo-tuberosum.

The dermatoses, induced by the internal administration of iodine, are, so far as they consist in erythemata, papular and vesicular, or urticarial and nodular erythanthemata and escapes of blood, to be ascribed to disturbances of circulation. The inflammatory iododerma appears chiefly in three forms—first, pustulo nodular; second, bullous (pemphigoid); and third, in tumour form (anthracoid). Of these the *pustulo nodular* demands most interest, as it is in general practically characteristic of the internal administration of iodine; indeed, like iodine catarrh and iodine headache, it is almost a "physiological action" on the human skin.

This view has been supplied by Adamkiewicz with an apparently scientific basis, by his recognition of iodine in the "acne pustules," for he, unfortunately using the popular name, iodine acne, allowed himself to be misled and to assume the seat of the disease, as in true acne, in the follicles. According to his view the iodide of potash is not itself to blame for the affection, but it is broken up by ammonia along with nitrogenous and a-nitrogenous free acids, which are formed in the sebaceous glands from the albumen of degenerated epithelia. To the iodine, which first becomes free in the contents of the sebaceous glands, Adamkiewicz believes he can ascribe all the appearances of the so-called iodine acne.

I shall go somewhat closely into this utterly untenable and long ago contradicted view, for many of the better text-books still seriously describe this form of iododerma in the same sense, and it teaches us further what an amount of false representations may depend on one single inappropriate name.

If we for a moment admit the observations of Adamkiewicz to be right, and iodine was found in all pustules of this iodine eruption, naturally not in quantities which can be weighed, but qualitatively recognisable, if even only in traces, as in the urine, saliva, the tears, and in the milk; this would not be so remarkable. The sebaceous

glands would then only act like many other organs in excreting drugs, though we usually attribute this power only to the true secreting glands with permanent epithelium. But the passage of the readily soluble iodine salts and the volatile iodine into the cells of the sebaceous glands, and the setting free of this substance in the physiological degeneration of the latter has nothing remarkable about it; it would rather be remarkable if, with the aid of very delicate reagents, we were not able at the same time to recognise traces of iodine in all the tissues of the body.

The question which is before us is quite a different one: are these traces of free iodine—Adamkiewicz himself does not ascribe it to the iodide of potash—able to induce the symptoms of iododerma pustulo tuberosum? It is very easy to answer this question, for we have an overwhelming clinical experience that iodine, externally applied in minimal or in maximal doses, never induces pustules and nodules (see iodine dermatitis). It cannot be objected that here quite other conditions are present, for we know that iodine deposited on the horny layer acts very rapidly, partly leucotactically, partly favouring the growth of the cells, as far down as the subcutaneous tissue, thus far below the level of the sebaceous glands and, in view of the volatility of iodine, certainly also inside them. The experiment, exactly in the sense of Adamkiewicz, has been carried on by everyone of the great majority of practitioners, when the iodide of potash ointment, which continuously gives off traces of iodine from the action of the fatty acids, is rubbed into the surface of the skin, where it of course enters chiefly into the follicles and sebaceous glands, in spite of which iododerma pustulo-tuberosum never develops.

Iodine does not, like croton oil, produce suppuration on its entrance into the follicles, but rather inflammation, that is when applied not in traces but in ponderable quantities.

But even this fundamental fact of this incorrect idea has not been confirmed; Pelizzari and Ducrey could discover no iodine in the pus, and the presence of iodine in the pustules is certainly not invariable.

The idea of a follicular irritation due to iodine in "iodine acne" cannot hold dermato-clinically either. Fox, captivated by this idea, regards the other inflammatory iodine dermatoses, especially the bullous, as magnified pustular eruptions. Morrow has already pointed out the impossibility of referring all these varied eruptions to the follicular apparatus. Duckworth reported a pustulo-tuberous eruption on scarred parts of skin in which follicles were no longer present; other authors have observed this form on the a-follicular palm of the hand. Then we must recollect that the so-called iodine acne has its own seats of predilection, which only partly coincide with those of

acne (nose, inner parts of the cheeks, and the sternum), but partly not (the one the shoulders and arms, the other the back and the upper margin of the face). If carefully checked the distribution of the pustulo-tuberous iodine eruption much more resembles that of seborrhœic catarrh than that of acne. All authors who have had the opportunity of histological examination—Thin, Duckworth, Pelizzari, Ducrey, de Amicis, Colcott Fox, and Gibbes—are completely against the follicular origin of the eruption, and—an important point—both their observations and their conclusions coincide.

Thin believes that all, even the pustular forms of iododerma, may be explained by the injury of the blood vessels by the iodine, from erythema to "iodine pemphigus" and even "iodine purpura." He examined a blister (not an actual pustule) and found a wide-reaching inflammatory change of the vessels and a defect of the vessel in the centre, which had led to bleeding; the sebaceous glands were normal.

Duckworth found on examining an iododerma pustulosum, the chief changes in the papillary body, which was flattened out, and very rich in new formed cells, the blood vessels were surrounded by emigrated cells, dilated but not torn. Hair follicles and coil glands were unchanged. There was a superficial inflammation leading to scar tissue, but no resemblance to the changes in acne.

Pelizzari found, in addition to the absence of iodine in the sebaceous glands, hyperæmia and cellular infiltration around their vessels, but maintains that a high degree of irritability of the vessels is the cause of the nodular form, as of the purpura.

Ducrey could neither find iodine in the pustules nor a process of inflammation associated with the sebaceous glands. According to him, iododerma is a trophoneurosis.

De Amicis places the origin of the inflammation, not in the glands, but in the papillary body, and considers the process therefore not as an "acne iodica."

Fox and Gibbes found that the inflammatory changes do not extend beyond the cutis, but begin in the form of inflammatory areas in the cutis, which pass into microscopic abscesses. The blood vessels are markedly dilated, sometimes plugged, the coil glands much changed, sometimes even partly destroyed; on the other hand, the sebaceous glands and hair follicles are only here and there secondarily affected by the inflammation.

According to these observations, which are in the main confirmatory, a primary alteration of the follicle apparatus appears to be quite excluded. We have to do with an inflammation, usually seated somewhat superficially in the skin, in which the vessels and their surroundings appear as cellular cords, and there develope in certain places,

through the assemblage of leucocytes, intra-cutaneous abscesses which may indeed occasionally burst through a follicle, though this seems never to have been observed histologically, and very rarely clinically. In the majority of cases a distinct co-affection of the papillary body by the inflammatory process was recognised, but there were never any peri- or intra-follicular abscesses, which at least would suggest acne.

But in spite of the agreement of these results, we are far from possessing a knowledge of the pathogenesis of the affection. Future investigation must be more closely directed to the development of the abscesses which appear scattered in the cutis, and to the possibility of bearers of infection from the epidermis and the follicles. For it cannot be denied that the internal administration of iodine, like the external application of diluted phenols, increases the disposition to the development of other distinctly parasitic pustular skin diseases and brings more rapidly to maturity any which are present. But if these external factors, such as complicating parasites of the epidermis and follicles, play any rôle in the pathogenesis of the affection, then from the first we cannot expect any definite agreement in the observations, and in explaining them we must proceed very carefully. This warning relates in a still higher degree to bromoderma.

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Bromoderma pustulo-tuberosum.

The pustulo-tuberous form of bromoderma has had the same fate as the corresponding one of iododerma, it has been regarded as an affection of the follicular apparatus, from a superficial resemblance to acne vulgaris, and the recognition of traces of bromine—in this case by Guttmann—in the contents of the pustules has been interpreted as a proof of an excretion of bromine by the sebaceous glands, to which the skin affection was due.

Against every one of these conclusions we have the same objections as in the corresponding form of iododerma. Even if Guttmann's discovery of bromine were to be again and again confirmed, it would be

quite irrelevant to the genesis of the affection; further, Veiel and other investigators could recognise no trace of bromine in the contents of the pustules with bi-sulphide of carbon and chlorine water.

The histological observations hitherto made are less in accord than in pustulo-tuberous iododerma. Neumann found a dilatation of the hair follicles, which were filled with horny masses, sebum and pus, their mouths sometimes open, sometimes closed. The papillæ were lengthened—presumably the prickle layer hypertrophied and the ducts of the coil glands dilated and cellular. In the cutis, Neumann noted a cellular infiltration around the glands and a scattered one through the papillary body, but evidently not of striking extension (see diagrams in his text-book).

Seguin dwells chiefly on the increased thickness of the prickle layer and a cellular infiltration and fibrous hypertrophy of the whole cutis. But he did not find the point of origin of the inflammation in the papillary body, the hair follicles or the coil glands, and in general no marked inflammatory changes.

Stephen Mackenzie observed hyperæmia, exudation of white and red blood corpuscles, especially in the region of the papillary body, small abscesses in the neighbourhood of the hairs and sebaceous glands, and small multi-locular vesicles in the upper layer of the epidermis.

Fox and Gibbes found on the contrary the chief changes again to be perivascular and in the neighbourhood of the sweat pores, and they consider the changes in the sebaceous glands as only secondary and unimportant.

We see that investigators of the pustulo-tuberous bromoderma dwell, more than in the iododerma, on the co-affection of the epidermis, and at least admit that of the follicle. Neumann described direct intra-follicular abscesses, Seguin's and Mackenzie's statements make probable an eczematous change of the skin surface, while according to Fox and Gibbes, the surroundings of the coil ducts are affected at their mouths. In a certain sense this co-affection of the superficial layers and the resultant variety of appearances corresponds with clinical experience, for the suppurating nodes of bromoderma are more polymorphous than those of iododerma. In almost all the cases which I have examined clinically, there existed a seborrhœic catarrh of the skin which was only accentuated by the simultaneous bromine eruption and in many places passed imperceptibly into it. This symbiosis of seborrhœa and bromoderma has moreover been already remarked by the oldest authors on the latter subject (Voisin, Veiel), and Veiel directly draws attention to the transition of a so-called dry seborrhœa into the bromine eruption. It is therefore not to be wondered at that the latter shares the polymorphism of the

seborrhœic catarrh and accordingly the histological appearances will also vary. If, with the necessary criticism in this direction, a larger series of pustulo-tuberous bromodermata were examined, the question would be cleared up how far the seborrhœic catarrh is necessary to the development of this form of eruption, and whether its peculiarities are explainable by this complication.

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B. NEUROTIC INFLAMMATIONS.

All this class of dermatoses belong most probably to the infectious inflammations. In the case of the neuroleprides, the neuro-syphilides, erythema nodosum, and zoster, this is beyond doubt; but the erythema multiforme of Hebra and the hydroa and herpetic forms have also a claim to this etiology. If I nevertheless separate them from the infectious dermatites it is because, as already indicated above, they do not appear to be pure infectious inflammations of the skin, but influences lying outside the skin, especially nervous influences, which, after the departure of the inflammation, play a rôle which is not evident in the pure infectious inflammations of the skin.

We can distinguish four groups in this class of inflammations. The first, the erythema group, contains some acute inflammations (Erythema nodosum, Erythema multiforme) and some chronic (Neurolepride, Neurosyphilide). Then comes the Prurigo group (Prurigo mitis, Prurigo gravis), which perhaps should also include the so-called Lichen urticatus, then the Hydroa group (Hydroa mitis, Hydroa gravis), and the Herpes group (Zoster, Herpes genitalis et facialis).

1. The Erythema Group.

This is a group of skin diseases, well defined both histologically and clinically, which I sharply distinguish from the angioneuroses and ally with those inflammations whose localisation in the skin, in addition to the simple appearances of inflammation, also leads to angioneurotic symptoms. The latter are indicated clinically only in the accompanying spastic œdema, which depends on an irregular innervation of the vessels leading to and from the part. For their likeness to the toxic angioneuroses, mentioned by other authors, consists only in relation to this œdema, while all the other characters of the pure

angioneuroses (connection with the circulatory elements, angiogenic symmetry, &c.) are absent. Our histological methods for methodically examining the essence of this matter are very deficient, for we are unable to study the peripheral vessel ganglia and nerves and their pathological changes. But these dermatoses have, in addition to the presence of a very sharply localised œdema, another common histological symptom, which distinguishes them as well from other forms of inflammation as from the pure angioneuroses, while it approaches them very near to the neuroleprides and neurosyphilides. They all present *an inflammation limited to the vessels and their immediate surroundings.*

The most important of this group is erythema nodosum, which I place first, for its infectious character is as certain as its anatomy is simple and clear. It may therefore serve to make plain the other allied diseases. To these belong especially the Erythema exudativum multiforme of Hebra with its familiar varieties, and Herpes iris, which, in common with Rayer, Hebra, and most recent authors, I regard as an individual sub-variety of Erythema multiforme. Possibly in the future we shall have to add to this group a rare affection of the fingers resembling pernio, but without perniosis.

(*a*). Acute Neurotic Erythema.

Erythema nodosum.

Cherry stone to cherry sized nodes and lumps of bluish red colour, which project somewhat over the level of the skin, but appear for the most part to be **in** it, not sharply margined by the healthy surroundings, but still palpable, and very tender on pressure. They always appear on the leg and the back of the foot up to the knee, are much rarer on the arm and the under part of the trunk, and appear usually in the number of one or two dozen, often with fever and articular pains. When they are present more numerously, the smaller ones have, particularly on the arms, a certain resemblance, from their superficial situation, to the papules of Erythema multiforme Hebra, but they never like these widen out concentrically on the surface, and never produce blisters and rings of vesicles. In place of that, they present a play of colours similar to that of hæmorrhagic nodes developed by contusion. The course is in slight cases ended in three weeks, in severer ones with relapses in six weeks; the nodules are absorbed, leaving pigmentation. Erythema nodosum does not appear in epidemics, and shows no tendency to recurrence.

The histological appearance of Erythema nodosum shows the character of the group most clearly. We find the whole vascular net of the cutis and the papillary body dilated and closely surrounded by densely packed cells, so that all sections of the vessels stand out from the only moderately cellular skin, like thick cellular cords. With a good protoplasm stain we see that this cellular mantle consists partly

of leucocytes and partly of swollen spindle cells in a state of mitotic division. Only here and there we see rounder large cells, with somewhat deeply staining protoplasm, but never true plasma cells. The leucocytes have sometimes a single round nucleus, sometimes clover-leaf-like fragments without any definite rule; the former may be found in the tissues, the latter often in masses still in the blood vessels, particularly the veins. They are sometimes so massed that they have the aspect of white thrombi. Beyond this perivascular cell mantle the cutis is only slightly more cellular than usual, and this increase is due chiefly to a mitotic proliferation of the ordinary spindle cells and a general swelling, whereby they assume more rounded forms. They often contain two nuclei. In view of this and the stagnation of leucocytes in certain parts of the circulation, the paucity of leucocytes in the cutis is very remarkable. This fact corresponds with the other that the immigration of wandering cells into the epidermis is almost nil. The latter participates in general in the process only with a general swelling of the cells, widening of the lymph spaces and numerous mitoses. Now and again in the course of the disease we may certainly have, in those nodules which have distended the skin somewhat more, a slight formation of scales, and in such places we find, from the papillary vessels outwards, a direct but always limited increased immigration of leucocytes into the epithelium, a very marked dilatation of the lymphatics of the latter, disappearance of the kerato-hyalin and widening of, and retention of the nuclei in the basal horny layer. But this affection of the epidermis plays quite a subordinate rôle in Erythema nodosum, while it almost distinguishes Erythema multiforme.

According to present day views on emigration, we must admit that the infectious germ which has embolically reached the skin, or the infectious substance proceeding from it, does not extend beyond the perivascular space, but from it is again taken up. According to the appearances developed in the neuroleprides, this means, that the infectious germ of Erythema nodosum does not thrive in the cutis itself, but only close around the vessels. But inside this perivascular lymph space it leads, not only to slight emigration and distinct cell proliferation, but especially to a marked œdema and the disappearance of the elastic fibres. The œdema spreads in diminishing quantity from the much-dilated spaces round the vessels of the skin into all the lymph spaces of the cutis, and leads to the general swelling of the skin which causes the nodes. The elastic net of the rest of the cutis remains, however, well preserved, and this explains the later complete recoil of the skin at the seat of the node, without any persistent relaxation. Mast cells are found everywhere in the cell groups and their neighbourhood, but not in particular abundance; they are mostly round and

often poor in granules, as if they were only in course of formation. Escapes of blood which would explain the discoloration during healing, I have not found. We must then attribute this coloration to the breaking up of hæmoglobin inside the blood vessels, which takes place in the stagnating blood column behind and in front of the white thrombi. The discoloration, moreover, like the white thrombi, varies in different cases.

Erythema exudativum multiforme (Hebra) *and Herpes Iris.*

Elastic œdematous papules of a bluish or vermillion red stagnation colour, rapidly growing, from the size of a mustard seed to a lentil, then remaining stationary, or spreading further in concentric arrangement. They are flat or somewhat raised, appear first on the wrists and backs of the hands, then extend over the fingers, forearms, dorsum of the foot, face, ears, oral mucous membrane and leg, always preferring the upper half of the body. The eruption is never universal and chronic (that indicates confusion with the erythanthemata) it has, like an acute exanthem, a typical, spontaneous course of two or three, in severe cases four weeks, readily recurs, particularly in autumn and spring, and then often in small epidemics. The exanthem differs from the erythanthemata through the merely regional symmetry, through the impossibility of provoking or revoking it by simple, external irritants (*e.g.* temperature), and further, that the papules neither at the commencement relate to the circulatory plane elements nor come into connection with them in their course. They often widen—and here every case shows on all spots the same tendency—concentrically, up to the size of a florin and more, the margin remaining lighter, up to vermillion red and somewhat œdematous, while the centre becomes bluish violet and flatter ; sometimes a second ring of œdema of a lighter colour succeeds the first (Erythema Iris). In other cases the peripheral border is covered with flat vesicles or a continuous vesicular ring, which advances with it, extending as much outwardly as it dries up inwardly ; then the centre is continually covered with fine scales (Herpes Iris). In place of the elevated vesicles there oftener ensues a mother-of-pearl grey, shimmering, bullous exfoliation of the horny layer, which also extends outwards. As the spots increase they may run together to polycylical figures (true Gyri on the contrary are only found in the erythanthemata, as are similar eruptions with urticarial development). Except slight burning and itching the eruption causes no further disturbance ; now and again it is complicated with pains and swelling in the joints. After healing deep pigmentation usually remains, which, in the iris form, may be in rings and cockades.

The histological examination of the simple, multiform erythema gives almost the same result as that of the vesicular and iris forms. In the latter cases the epidermic changes are more pronounced and confirm the macroscopic appearances. So far as concerns the changes in the cutis we have, as in erythema nodosum, altogether four different symptoms : dilatation of the vessels, cell proliferation around the vessel walls, emigration, and œdema of the cutis, only they are present in different distribution. The affected region is here, not the whole

cutis, but mainly only the papillary body; in certain papules the process extends in the centre somewhat along the vessels. In this superficial expansion we find dilatation of the vessels and proliferation of the perithelia. The emigration is more active than in Erythema nodosum and arranges itself in a straight line from the sub-papillary vascular net outwards towards the epidermis, which is sometimes profusely infiltrated with leucocytes. Moreover, the emigration here is in general not so marked, as specially limited only to certain points. The œdema is here evidenced, less in a distension of the larger lymph spaces as in erythema nodosum, than in a general swelling of the papillary body. The collagenous tissue of that part is much swollen, quite transparent and unstainable, the elastic substance is hardly any longer recognisable, the protoplasm of the connective tissue cells only stains faintly. This œdema reaches generally from the sub-epithelial vascular net to the epidermis and doubles or trebles the thickness of the papillary body.

Then there is added, an œdematous swelling of the epithelium and a dilatation of its lymph spaces—changes, which are also present in superficially placed nodules of Erythema nodosum, and further a not inconsiderable epithelial proliferation. It is evident that these last three changes—emigration, œdema of the papillæ, and epithelial growth—do not attain their highest development on the same place, but that on the contrary, where the papillary swelling is most marked not only no epithelial proliferation exists, but the emigration of leucocytes into the epithelium is almost completely absent. On the other hand, the seats of the most marked acanthosis correspond to the most profuse emigration.

The comparison of tiny punctiform with somewhat larger papules in which one can distinguish a bluish white border, teaches us that the papillary swelling is the first of these three symptoms, and that acanthosis and emigration first appear, where the maximal œdema of the papillæ has again grown less. The white advancing border of the papules corresponds to a triple or quadruple ring of papillæ, which are distended by œdema into knob forms and over which the still unaffected epithelium runs, somewhat flattened. The centre which has returned to the level of the skin and, compared with the margins, is somewhat depressed, corresponds to an always increasing area of moderately œdematous papillæ which, by the proliferating epithelial ridges, are narrowed, made smaller and flattened out. At the same time profuse immigration of leucocytes takes place at different points into this advancing epithelium. There also often appear, at the summit of the papule, small vesicles, which are purely inter-cellular in their nature, and form directly under the horny layer from the

displacement and compression of some rows of prickle and granular cells. They are at first filled with serum but later usually receive an immigration of leucocytes and then dry up to a small cellular crust, while the whole epithelium here readily scales.

The infectious germ which, in Erythema multiforme, passes from the circulation into the cutaneous tissue induces then, first, severe œdema and later cell proliferation and a moderate emigration; only it is characteristic of this affection, in contrast to Erythema nodosum, that these changes take place only on the surface of the skin, over which, however, they extend for some distance concentrically. We must, consequently, conclude that the poison partly spreads itself along the sub-epithelial vascular net, but is partly also conveyed by the lymph stream into the lymph spaces of the epithelium; for otherwise it would be very difficult to explain the diffuse severe immigration of leucocytes there.

Of other appearances there are still worthy of mention: short, white thrombi, which preferably have their seat at the points of those blood capillaries which present very severe œdema, and perhaps have a share in its development, and a very small number of mast cells. Mitoses in the perithelium of the blood vessels are readily recognisable, here and there also in the endothelium; they are very numerous in the epithelium. Underneath the superficial vascular net the cutis is almost normal, except that the vessel trunks present a greater richness of cells in the adventitia.

To this sketch of the main type we can easily add those histological factors which are characteristic of the special development of Herpes iris. The shining mother-of-pearl, greyish white colour which the edge in that case often shows is not caused by a slight bullous elevation, but by a very marked œdema of the deepest prickle layer. Then the nuclei of the under rows of the epithelium are found pushed outwards, while the protoplasm at the proximal end of the cells is much swollen, will not stain and appears liquefied, so that, with powerful protoplasm stains, there seems to exist in this part of the prickle layer a net-work of cell membrane, although really not a single epithelial cell has fallen out or degenerated. I regard this appearance only as a high degree of œdema of the basal prickle layer, in direct contact with a similar one of the adjacent papillæ. This must induce a strong white reflexion and very effectually conceal the vascularity of the skin.

Where there is actual vesicular development on the border of the eruption, we find a marked widening of all the lymph spaces of the epithelium, and on certain spots dilatation into a sub-corneal vesicle, containing pure lymph. In many eruptions this extends with under-

mining of the horny layer and neighbouring vesicles to a larger monolocular blister, under which the prickle layer is simply compressed without undergoing in any sense degenerative changes. Then the blister dries up to a flat scale, the exudation being purely serous can be readily absorbed, it contains neither enough fibrin nor leucocytes to form a crust.

Herpes iris appears to be accompanied by greater proliferation around the vessels and to cause a more lasting eruption, which, after recovery, leaves a very deep persistent pigmentation in the cutis. This, under the influence of the greater epithelial proliferation and leucocytosis, disappears more in the centre than on the border, and therefore often persists in the form of brown rings.

(*b*). Chronic Neurotic Erythema.

Neuro-leprides.

By neuro-leprides I understand all those affections of the skin caused by the lepra organism, which owe their development not—like the lepromata—to the direct attacking of the cutis tissue, but indirectly to its growth in the cutaneous nerves. The lepromata (see that chapter) are developed in those lepers whose whole cutis supplies a good nutrient medium for the bacilli; the neuro-leprides in those persons whose skin in general does not permit the growth of the lepra bacillus, but whose nerves do. Mixed forms are throughout rare, and never form the regular type; one finds oftenest scattered circumscribed lepromata developing on neuro-leprides and subcutaneous lepromata as complications. Many of the cases, so-called mixed, are true papular neuro-leprides in which the prominent elevations are incorrectly considered as lepromata. Both developmentally and histologically lepromata and neuro-leprides are absolutely different.

In addition to the basal separation from the lepromata the comprehension of neuro-leprides requires the constant separation of the primary angio-neurotic and the secondary embolic elements. In the following description I refer first of all only to the former.

The neuro-leprides appear, either gradually, limited to certain areas of predilection (forehead, cheeks, ears, chin, and extensor surfaces of the extremities) or suddenly, all over the body (with the exception of the hairy scalp, the palms, and soles), in the manner of an acute exanthem, but in all cases strictly symmetrically. The symmetry relates not only to whole regions of the body (such may also be found in lepromata) but often permits a perfect identification of symmetrical vascular regions, particularly seen in the universal erup-

tions on the back. The eruption consists of hyperæmic spots or rings, in size that of a lentil to a florin or the palm of the hand, whose redness, where there is general pigmentation, is concealed by a hyperchromia. In the ring form the centre is pale, uncoloured, and often from the commencement anæsthetic, while the hyperæmic spots and zones show sometimes anæsthesia, sometimes hyperæsthesia.

Once developed, these spots have an almost unlimited duration. The later changes consist mostly in a papular thickening and greater pigmentation of the previously hyperæmic zones. Their margins at first somewhat sharp (never so sharp as in leproma) become in time somewhat obscure, and thus neighbouring spots and rings run together. But an extension of the rings, like a serpiginous syphilide or lupus, never takes place.

The neuro-leprides, even where the skin is much thickened, never distinctly elevate themselves (like the lepromata) over the level, and never lead to the falling out of the hair, and thus neuro-lepers are as readily recognisable in the distance by the persistence of the eyebrows, even with thickening of the skin of the part, as by the regular anodular thickening of the ears.

As new vascular areas are affected there develop gradually, particularly on the face, forearms and hands, legs and feet, flat rednesses and thickenings, always combined with œdema and cyanosis. On the legs and hands this goes on to elephantiasis, to epithelial growth, diffuse scaling, dropping off of the nails, and congestive ulcers.

It must be distinctly noticed that there is no proportion between the spread and amount of this exanthem, and the perceptible nerve lepromata which always accompany it.

Quite independent of this angio-neurotic basis of the neuro-lepride are the bacillary emboli, which, in the course of lepra, take place in the same areas of skin. When these affect skin previously free from neuro-leprides as subcutaneous pale nodules or cutaneous, bluish red, somewhat elevated, painful, inflammatory papules, they readily and rapidly disappear again without leaving the germ of a permanent eruption. But if the emboli affect macular neuro-leprides these swell up, and a distinct thickening persists, which may independently advance. The "macular" neuro-leprides are converted into "papular," roseolæ into papules, flat erythemas into flattened thickenings of the skin. Under treatment, the papular neuro-leprides relatively easily become macular, while the macular basis is much more difficult to manage.

From the papular neuro-leprides, true lepromatous nodules now and again develope, most frequently downwards—subcutaneous lepromata, more rarely upwards. In the latter case, these cutaneous leproma nodes which are quite isolated on the diffuse neuro-leprides are easily

distinguished from the latter. Such scattered lepromata hardly entitle us to class the whole cases as mixed.

These angio-neurotic exanthems hitherto described, constitute a distinct variety of the neuro-leprides, the spotted lepra (lepra maculosa Hansen) which usually remains as such, and more rarely passes into the other form of nerve lepra (Lepra atrophica): mutilating leprosy. The nerve lepra may take one of two courses, of which one presents in addition to slight anæsthesia a very multiform exanthem, the other with very indefinite eruption (this is sometimes completely absent) very widespread disturbances of sensation, and as a result of this, the most marked trophic changes. This lepra atrophica we shall consider again in the chapter on regressive changes. The disturbance of the skin which accompanies it at the commencement is an eruption of vesicles, the so-called *Pemphigus leprosus*, the specific neuro-lepride of the atrophic lepra. Between these two forms of nerve lepra there are naturally very many distinct transition forms, as between the nerve and skin lepra. The appearance of atrophic symptoms in papular neuro-leprides is often incorrectly regarded as a transition of skin into nerve leprosy.

The next distinction of the neuro-leprides, which I have made from clinical experience, is into an angio-neurotic basis, and a secondary bacillary development, two stages which correspond pretty well with the clinical forms of the macular and papular neuro-leprides; and these have been confirmed histologically by Philippson in my laboratory. After Pollitzer discovered, in 1889, the presence of bacilli in the papular neuro-leprides, a discovery which has been regularly confirmed since, Philippson succeeded in establishing that in fresh embolic papules, older progressive changes in the larger vessels of the affected part were always present, so that one could definitely distinguish chronic, particularly located in the depth of the skin, and acute conditions of inflammation, chiefly on the vessels of the papillary vascular system. In particular the relation of the bacilli towards themselves and towards the tissue was for both zones characteristic and very different. Further, he obtained convincing appearances of the clinically so remarkable rapid disappearance of the superficial acute symptoms of inflammation, which were evidently due to the destruction of the bacillary masses.

Chiefly supported by these and earlier examinations of my own, I venture to present a more exact demonstration of the genesis of the neuro-leprides. This can be better attained than in the true leproma (see that chapter) as here the stages of the development are much further apart.

The Angio-neurotic Basis.

The confirmatory material comes chiefly from one of my cases, in which, on the husband of a leprous woman who was under control, there suddenly developed a limited circumscribed neuro-lepride as the first sign of leprosy, in the form of a spot on the forehead and a ring on the back of the foot, anæsthetic in the centre and about the size of a shilling. The latter can not have been more than ten days old when it was extirpated.

The chief changes are located round the vessels of the cutis, corresponding to the centimetre wide, red border of the ring; all the capillary vessels are dilated and surrounded by a mantle of hypertrophic connective tissue cells. This change is naturally most striking where the capillaries lie most closely in the papillary part of the skin, and then in the neighbourhood of the coil glands. There was found neither an emigration of leucocytes nor any emboli of bacilli, nothing but scattered bacilli on the endothelium of the arteries and capillaries. We have before us a simple uncomplicated hypertrophy of the adventitial connective tissue, in which chiefly the cells, but also the inter-cellular collagenous tissue, share. Only in the middle of the affected part does this hypertrophic alteration extend somewhat further from the capillaries into the surrounding papillary tissue, so that one has here, in place of scattered strings of vessels, a papillary body, somewhat hypertrophic over all, which may be recognised clinically through an increased resistance of the part.

Compared to this perivascular change in the capillaries of the cutis and the papillary body, the arteries and veins of the cutis are almost, and those of the hypoderm completely free from adventitial thickening.

On the contrary there appears here at the under margin of the cutis—and my material does not reach much further—another appearance as an addition, namely a marked thickening of the nerve trunks, which is due to a hyperplasia of all their connective tissue elements. The thick usually twisted or spiral cords closely resemble the corresponding nerve cords in neuro-fibroma. The search for bacilli, was, except for one single tiny clump of bacilli in the perineurium, negative. At all events the presumptive invasion of sensory nerves did not reach into the cutis. A more thorough investigation of all the cord-like structures in the cutis showed in addition that the vessels, cords, and sometimes in addition to them the nerve fibres penetrating the cutis perpendicularly, were also accompanied by a hyperplastic connective tissue sheath.

To sum up: a chiefly cellular hyperplasia of the vessels of the

cutis as well as the connective tissue constituents of the hypodermal, less of the dermal nerves, and an almost complete absence of bacilli.

I have given this detailed description because here clinical observation allowed us with certainty to exclude every previous leprous skin affection, either general or local. The numerous neuro-leprides with or without bacilli which I have had the opportunity of examining during the last eight years, were in relation to their previous history never so certainly absolutely fresh. While the chiefly cellular nature of the vessel changes in the cutis gives the impression that it has only lasted a short time, and the acute development of the erythema does not contradict the histological appearance (mitosis could certainly not be observed), the thick nerve cords of the hypoderm allow of no other explanation, than that here a parenchymatous neuritis has for a long time existed. It corroborates this discovery that, in addition, now and again later spots appear on already anæsthetic areas.

But if here (and everywhere else) a bacillary affection of the nerve trunks has existed before the skin affection appeared, this latter is capable of different explanation.*

On the one hand the hyperplasia of the vessel might be looked upon solely as a result of its paresis from pressure of the nerve leproma on the vessel nerves, without the bacilli coming into direct contact with the capillaries of the skin. This view would correspond to the absence of bacilli in the cutis. The few bacilli in the nerve sheaths at the cutis margin would appear as advance posts of the nerve leproma.

Or one might regard them as a generalised embolisation of the skin from the already existing nerve lepromas, which had passed over without leaving any trace except on the two areas of the skin, which a nerve paresis has transformed into a favourable soil. But here a clinically recognisable erythema and histologically a vessel hyperplasia would immediately have been the result. But the bacilli had, in consequence of the reaction of the skin at once been destroyed. In this view neurotic and bacillary theories are put in their proper relation, and though it appears somewhat complicated it certainly corresponds to the easily constituted facts of re-embolisation on the older neuro-leprides, to be described immediately. But I can in addition place in the scale the following fact in favour of this view. In all the coil glands, without exception, which are visible in the sections of this neuro-lepride, the epithelium is thickly permeated with those granules and clumps of granules, which share the reaction and acid resistance of the bacilli, and which I long ago demonstrated as bacilli, altered by the secretion of the coil glands.

* A bacillary invasion of the skin by way of the sensory nerves can be excluded by other here irrelevant grounds.

As these granules of vegetable origin are absent in the coil ducts and on the surface of the skin, but on the contrary are present in the lymph spaces immediately around the glands, one must conjecture a breaking up, or at least a morphological change of the bacilli by the coil glands, and while this discovery was only previously known of leproma it evidently accompanies the very first leprous cutaneous symptoms.

The examination of numerous older neuro-leprides taken from anæsthetic, unpigmented, and hyperpigmented spots, teaches, that the description given, so far as it concerns the hyperplasia of the vessels and the absence of bacilli, possesses a very general application. But it was only exceptionally that I was able to recognise on old spots the inflammatory thickening of the subcutaneous nerve trunks, it may be that it had passed by or that only more central pieces of nerve had been affected. The granules described in the coils also are always absent in old macular neuro-leprides.

The other constituents of the skin show slight or no changes. The muscles and the elastic fibres, the hairs and sebaceous glands, are quite normal. The surface epithelium is usually somewhat thinned and slightly stretched by the inflammatory swelling. The collagenous tissue is in general normal, but around the capillary blood vessels, and as far as the cellular hyperplasia reaches, it is mostly distinctly thickened or at least swollen and usually stained deeper than in the rest of the skin. At all events the rarefaction and atrophy of the collagenous connective tissue which is present in the lepromata is completely absent, the enlarged protoplasmic connective tissue cells remain spindle formed and acquire neither the form nor the dimensions of plasma cells and chorio-plaques. The neuro-lepride presents throughout the character of pure hypertrophy.

The Embolised Neuro-lepride.

With very slight general symptoms, often with fever, there appear in certain or on all neuro-leprides changes which present themselves clinically as œdematous swellings with hyperæmia and escape of blood colouring material. The yellowish or bluish-red flat, somewhat painful thickenings have the form of pea or lentil-sized papules or larger papular rings which only slightly project above the level of the skin. Even between older neuro-leprides on apparently healthy skin, such eruptions of the nature of multiform erythema tend to appear in general embolisation. But these in many cases indicate only the seat of unnoticed vessel hypertrophies dependent on nerve lepromata. At all events only such predisposed vessel regions react with distinct swelling, while on less disposed areas of skin the bacilli at once disappear, without inducing definite clinical symptoms or only inducing

pale, more tangible than visible, slight œdema, which rapidly and completely again disappears. This papular erythema, appearing with the signs of acute inflammation and only disappearing up to a certain degree is a sign that the embolus has reached an exceptionally favourable region for the growth of the bacilli.

With the appearance of these the time of blood circulation for the bacilli is already over; at least examinations undertaken at this stage give a negative result. But the embolisation of the skin is more surely proved than by this means, by the histological appearances of the skin itself, which we owe to the examinations carried on in my laboratory by L. Philippson. Over the whole region of the papillary vessels in this particular spot, all the capillaries are plastered with single bacilli and collections of them, sometimes they contain whole swarms, thrombi of bacilli. On other places thrombi of white corpuscles close the capillaries, so that where white blood corpuscles have collected no bacilli are found in the lumen, and vice versa. There exists also, what moreover the whole history of lepromata teaches, not the slightest attraction of the bacilli for white corpuscles. The scanty white thrombi may be rather quite simply explained by the hindrance to the blood stream which the bacilli induce, in that behind them the leucocytes remain deposited.

The walls of the blood vessels stand out more plainly than usual, cells and inter-cellular substance are swollen with serum, the lymph spaces directly round the capillaries are dilated, and the lymph vessels lying near, particularly near the surface, are much dilated. The nuclei of the endothelium and perithelium are multiplied; scattered mitoses, particularly of the former, are to be noted. Scattered bacilli penetrate into the dilated lymph spaces, multiply to close, parallel-lying clumps (like cigar bundles) and fill the lymph spaces of the peri-vascular, already existing cell infiltration. Emigration of white corpuscles is never seen, indeed they are so rare in the tissue that one must conjecture a paralysing or negative chemotactic influence of the bacilli on them.

A very similar appearance is found in all fresh embolised neuro-leprides. The differences concern chiefly the greater or less filling of the peri-vascular lymph spaces with older leprous material, the remains and the results of previous emboli, and depends thus altogether on the age of the affection, and further whether the eruption is still in progress or already in retrogression. L. Philippson has shown that in every fresh, embolised neuro-lepride the new immigration is easily distinguished from the bacillary colony already present. The first consists of single bacilli and small closely-packed clumps, the latter have long ago developed glœa masses in the lymph spaces, in

which the bacilli assume coccothrix forms (see leproma). One can, according to the differently marked distribution of older viscous bacillary masses divide the neuro-leprides into three grades or stages of development.

(α). **Recent forms.**—Here, in the depths of the skin, are found vessel cords with few clumps of bacilli of older date, while the superficial vascular net is evenly surrounded by viscous bacillary masses. In my available material which comes from recent lepra cases this appearance is very frequent. It is in its favour that the emboli affect chiefly the peripheral distribution of the cutaneous vessels, and that only later, it may be directly from the vessels by diapedesis, it may be from the capillaries along the adventitial lymph spaces, the deeper arteries and veins are surrounded by lepra masses. On many capillaries the leprous new formation is only formed on one side, it is the same on some of the larger vessels and then mostly on the side towards the hypoderm. Rows of bacilli independent of the vessels are never found.

(β). **Older forms.**—The cords filled with the old lepra masses have distinctly increased in number and calibre. At the level of the superficial vascular net they often run together to a regular layer. But the breadth of the cutis shows a net, formed of thick isolated cords, inside which the lepra-free regions stand out sharp. Around the hair follicles and coil glands the columnar, united cords tend down to the hypoderm and extend around the larger vessels or nerves or certain fat lobules. The new formation limits itself particularly to the blood vessels, clothes certain organs of the skin, hair follicles and coils, completely by means of adventitial cords, but follows also with small branching cords the nerves of the cutis, to end with them in the muscles and vessels. On account of the immunity which the muscles enjoy the bacillary nerve infiltration may sometimes be followed until close upon them, where it abruptly ceases. By following single nerves from the surface downwards, one can often determine that the smaller intracutaneous stretches of nerve contain in addition to the cigar bundles of young bacilli a great quantity of viscous older ones, while the subcutaneous stretches of nerve only present the younger ones and none of the swollen ones in their lymph spaces. Most striking in these older neuro-leprides —and characteristic of them in contrast to the leproma—is the sharp almost linear margining of the bacillary cords. One can thus define the older, like the younger neuro-leprides, as cord-formed, chiefly perivascular lepromata.

(γ). **Older forms with transition to subcutaneous lepromata.**—The method of transition into hypodermal lepromata of diffuse exten-

sion takes place along the cord—like processes of the older neuro-leprides into the hypoderm, which were mentioned under β. The sub-cutaneous tissue of neuro-lepers is indeed in general better disposed than their cutis. The extension under the skin can affect diffusely and regularly the fatty tissue or take place along the centripetally running veins and nerves in the form of broad, twisted bands. It may in certain places lead to large firm, subcutaneous nodes which raise the cutis in the form of large lumps. But in these cases there almost never takes place a union with the cutis, an extension into it, but over the sub-cutaneous nodes runs the corium, thinned and stretched, but still showing its old neuro-lepride as reticular branching cords.

This combination of sub-cutaneous lepromata with cutaneous neuro-leprides is very frequent and comprises most of the diffuse thickenings of neuro-lepers.

(δ). **Older forms with transition to cutaneous lepromata.**—The full development of this combination is very much rarer than that described under γ. The commencement of this may be found in the microscopic welding of a few sub-epithelial vascular cords into a small "parchment leproma," a somewhat more frequent occurrence. The growths diffusely infiltrating the whole cutis and transforming it to a hard tense semi-circular tumour are only exceptional in the skin of neuro-lepers. One can always definitely recognise on sections through such nodes their different origin, that the node at the periphery passes into ever finer cords, while the true leproma is, even microscopically, sharply defined from its surroundings.

Since I shortly define the embolised neuro-leprides as peri-vascular, cord-like lepromata, their internal structure will be found under that heading. I will here only shortly determine where they correspond and show the slight differences. Here also the collagenous tissue is pressed asunder by the masses, the elastic fibres disappear and the cell protoplasm is largely atrophied and replaced by bacillary mucus. According to the age of the neuro-lepride the quantity of connective substance or the bacillary mucus predominates, according to the presence or absence of fresh emboli, there are present or not, fresh bundle-formed colonies of bacilli, poor in glœa. The differences depend on this, that in the neuro-leprides the large plasma cells, the daughter cell areas arising from them and the giant cells are less frequent, as are the large much-developed clumps of bacilli. There are always found, even on the younger embolised neuro-leprides, particularly round the hair follicles, larger and smaller chorio-plaques, which differ from tubercular giant cells by the less sharp margin, the irregular position of the nuclei and the indistinct net-work of protoplasm.

In reference to the relation of the masses of bacilli to the cells I must refer to what is said under leproma.

The mast cells are less numerous in the neuro-leprides than in the lepromata, but more numerous than normal. Collections of them with degenerations, as in old lepromata, I have not found.

The important difference between the embolised neuro-lepride and lepromata lies in this, that even at the height of the first the bacillary infarct only permeates the cutis in the form of cords, while on the other hand the connective tissue scaffolding is not so severely affected by pressure atrophy as in the lepromata. While in the latter the tumour formation is to be attributed almost entirely to the swollen masses of bacilli, and the atrophy of the skin becomes evident on their disappearance, the embolised neuro-leprides retain, during their whole duration, their position at the stage of a slightly hypertrophic tissue.

The spontaneous or artificial disappearance of the embolised neuro-lepride brings it back again to the permanent condition of the angio-neurotic basis. L. Philippson has observed the spontaneous disappearance, in a slightly-disposed part of the skin (the shoulder of a patient, previously free from apparent leprosy on this part) within twenty-four hours of the development of the embolism. All the lymph spaces of the tissue were strikingly dilated, as were the lymph vessels of the upper layers of the cutis. Perivascular, evidently old, because already mucoid bacillary masses crumbled in these widely-open lymph vessels, breaking down into their individual, ovoid, mucous elements, so that the otherwise free lymph vessels were here, under the influence of acute inflammation, filled with loose masses of bacilli from the tissue.

Similar pictures of loose masses of bacilli in the usually free lymph spaces of treated neuro-leprides I would explain analogously as a simple mechanical transport of viscous organisms from the lymph spaces. The details of other changes, after chemical and physical treatment, are here irrelevant. But the result is always the same; the perivascular glœa masses disappear, the lymph spaces remain dilated, and the vessel strings resume the smaller dimensions which they had before the embolisation. During these regressive changes the skin always tends to greater pigmentation. One finds pigment in the wide lymph spaces of the cutis, still more in those of the epidermis. Corresponding to the disappearance of the bacilli from the nerves, the anæsthesia tends partially to disappear. A cellular infiltration of the vessel sheath remains as the remnant of the neuro-lepride, even when it has completely disappeared clinically.

Neuro-syphilides.

These form a complete analogy to the neuro-leprides. Although the recognition of the syphilis bacillus in the nerves of the skin has

not yet been accomplished, the clinical and histological correspondence compels us to place the latter with the neuro-leprides, and to separate them from the other syphilides, which correspond to the lepromata of the skin.

The neuro-syphilide usually appears first in the later secondary period, more rarely towards the end of the primary, and still more rarely in the tertiary, and may be best divided into four sub-varieties: 1. erythematous; 2. erythemato-papular; 3. erythemato-pigmented; 4. primary pigmented. All these forms resemble each other and differ from other syphilides through their correspondence in form with the circulatory plane elements of the skin or of the collateral net, their constancy to this place, their striking duration, their resistance to antisyphilitic remedies, and their erythematous form, and further, through the marked influence of external irritants to the circulation on the prominence of the eruption.

(α). *Erythematous Neuro-syphilides.*

These appear almost exclusively in the later secondary period, in the form of single symmetrical spots (the size of a threepenny, a shilling to two shillings), rings, semi-circles or larger segments of circles and of a bluish, red colour. They are seated on the trunk and extremities, especially on the shoulders and the neck. Sometimes these rings surround, more or less completely, smaller central spots. They disappear after months of existence, spontaneously or as the result of specific treatment, with or without leaving behind them pigmented spots and rings. According to their varied forms and late appearance they have been named: Roseola annularis, circinata, Roséole tardive.

Here also we find—as in the simple roseola—changes on all the vessels of the cutis, but of another character, in that, from the commencement there is, in addition to the cellular hyperplasia of the vessel walls, a hypertrophy of the collagenous intercellular substance—a sclerosing of the vessel wall. This is particularly developed on the superficial vascular net, less on the deep, and on the twigs to the coil ducts. This sclerosis gives to the strings, into which the vessels here also are transformed, quite a peculiar appearance. They look like solid, cellular connective tissue cords, so contracted is the lumen by the presence of numerous mitotically dividing spindle cells and new formed fibrillary bundles, in the usually so loose tissue lying alongside the capillaries. A swelling of the endothelium—mitosis are, on account of the chronicity of this hyperplasia, easily recognisable—aids in limiting the blood stream in the arterial capillaries. The venous capillaries possess wider lumina, but likewise swollen endothelia and hyperplastic stiff vessel walls, much thicker than normal. These circumstances explain the pale rose colour, the weakly developed stagnatory hyperæmia of the affection and its remarkable chronicity.

The cutis surrounding the vessels is only slightly richer than usual in spindle cells, and otherwise normal. Plasma cells are never found, mast cells very rarely, but on the contrary the leucocytes are rather more numerous than normal. The epithelium takes no share in the process, but appears stretched and atrophic.

The whole process may be regarded as a simple hyper-nutrition of the cutaneous vessels, as a result of the paresis induced in them by a syphilitic affection of the vascular nerve system. The hyperplasia and sclerosis of the vessel walls is simply the natural self-protection of the vessels against the increased supply of blood. To the absence of the infectious germ in the skin itself corresponds the absence of plasma and giant cells, which otherwise accompany all other chronic syphilides.

(β). *Erythemato-Papular Neuro-syphilide.*

A simple erythematous neuro-syphilide always locally precedes this rare form. Very slowly, unnoticeably, the spot or ring raises itself over the surface of the skin, acquires a darker, more yellowish red or brownish red colour, and presents to the finger a definite resistance, which, however, loses itself in the healthy surroundings; in this it rather resembles the large than the small papular syphilide. The obstinacy of the eruption which, in its isolation, form, symmetry, and the time of its appearance throughout resembles the simple erythematous neuro-syphilide just described, is still more marked, and its transition into the pigmented form frequent.

The histological appearances of the papular neuro-syphilide resemble those of the erythematous. The hyperplasia of the spindle cells and the hypertrophy of the collagenous adventitial tissue is still greater, especially in relation to the sub-papillary vascular net. As the hyperplasia of the vessel walls steadily extends to the connective tissue around, the vascular cords are transformed into plump cylindrical structures, which, however, always indicate their origin by the concentric arrangement of the connective tissue and the frequent presence of a lumen in the centre.

Thus almost all the connective tissue of the papillary body passes gradually into a firm peri-vascular tissue, containing spindle cells and collagen but no elastic tissue; only here and there, usually separated by a broad lymph space, some connective tissue is still evident, presenting the original looseness and fibrillation; both where the thick vessel cylinders cross each other or approach, and here and there along the sub-epithelial layer, margining the dense vascular cord of a papilla. But in other places the loose structure of the sub-epithelial streak is lost, so that the thickened connective tissue cell directly margins the epithelium, and a papillary body of the normal fibrillated structure no longer exists. It is of course evident that the form of the papillary body has before this disappeared, in that a few papillæ

are much widened through the cylindrical hyperplasia of the vessels, and have united at the bases, with neighbouring papillæ; others are completely laterally stretched and flattened. The epithelial ridge net is correspondingly flattened out, except for fine, pointed short remnants, while on the other hand the supra-papillary prickle layer is constantly more and more stretched by the pressure of the papule as it forms, is flattened, and finally becomes quite atrophic.

The cylinder cells then disappear over considerable areas, as they usually do only over the apices of the papillæ, and give place to small cubical ones. The remaining small band of prickle cells is still penetrated by numerous dilated lymph spaces, and always contains a considerable number of wandering cells. But the whole of the thickened cutis, corresponding to the stagnatory character of the circulatory disturbance, is permeated by an abnormal quantity of leucocytes, which never aggregate, and even in the rarefied epithelium, form no nests. The keratinization of the latter is perfectly normal; neither here nor in the connective tissue are there any signs of saturation or liquefaction; it is a dry pressure atrophy of the epithelium, caused by a similarly dry hyperplasia of the connective tissue.

At the height of the formation the whole papillary body, as well as a marginal stripe extending downwards beyond the superficial vascular net, has passed into a homogeneous fibro-cellular new growth, in which—inside the fibroma—the vessel lumina, with the swollen endothelia, stand sharply out. The new growth extends downwards along all the blood-vessels, rapidly diminishing in breadth, without presenting any other constituents but spindle cells and fibrillary bundles. In the under part of the cutis the spindle cells in the normal connective tissue are increased in number and size.

(γ). *Erythemato-pigmented Neuro-Syphilide.*

The erythemato-pigmented or secondary hyperchromatic neuro-syphilides develope exactly on the seats of the erythematous, or more often of the already papular form. The pigmentation usually appears first when the erythema is already gone or the papule flattened down; but now and again a deep-brown pigment is added to the still persisting neuro-syphilide. Then the pigmentation begins usually in the centre, so that, in course of time, a red margin encloses a pigmented spot, or in spots surrounded by rings, a brown centre is enclosed by a small hardly-pigmented border, and this again by a dark red, sometimes elevated broad border. These neuro-syphilides are described as the cockade and iris forms. The pigmentation usually lasts unchanged for a long time.

In the pigmented papular neuro-syphilides in my possession the pigmentation is only excessive inside the epithelium, not inter-epithelial in the lymph spaces, but only in the cells, and usually in their distal, more rarely in their proximal parts. Usually only the two lower rows contain pigment, and this is in the form of parallel rows of golden yellow granules in the outer rim of protoplasm. Especially rich in pigment were the remains of the old epithelial ridges. Should this be found, on further examination, to hold in all cases, it would present a notable difference from the primary pigmented neuro-syphilide.

(δ). *Primary pigmented Neuro-syphilide.*

The primary pigmented neuro-syphilides appear in two different forms, either as *brown spots* of the size of the plane elements, or as rings and segments of rings, which correspond exactly to the primary hyperchromasia of the neuro-lepers, but are much rarer. Or—and this is much more frequently the case—there appear, on certain areas of predilection, neck, axillary folds and sides of the abdomen, *diffuse smoky pigmentations,* which at once, in the regions of the plane elements, clear up, and thus—secondarily—disclose *pigmented nets;* the Rete pigmentosum of Syphilitics. This affection is most common in women, and recently, in ignorance of the true state of affairs, has been miscalled leucoderma syphiliticum. The white spots which appear on the dark ground of the primary diffuse pigmentation, have, as my ten years' study of the affection has taught me, absolutely no necessary connection with the bygone embolic exanthem of syphilis (Roseola, papules). It is an independent neuro-syphilitic exanthem, which may appear at the same time as other syphilides, but equally readily at another time, in the late secondary, indeed even in the tertiary period, on skin, which up to then appeared absolutely healthy. In the former cases one will certainly find places where a roseolous spot, or a papule, corresponds accidentally with a whitening plane element, without being strictly limited to its margin (on the neck the occasional roseola spots are usually larger than the very numerous small plane elements); but the majority do not correspond, but rather prefer the dark collateral net, or are often found partly in both. If a whitening plane element developes under such circumstances on the border of a roseola or papule, it cuts a rounded segment out of the spot, and the papule may even appear as if nibbled by neighbouring plane elements.

As a fact, the rete pigmentosum of syphilitics corresponds exactly with the appearance of Livedo annularis e frigore, but only in a certain stage of development. For the ring-formed blood stagnation is a rela-

tively constant appearance, varying only in a narrow boundary; and where it has the opportunity of forming, the anatomical margin between vessel cone and collateral net is, with the capillaries filled, brought directly and repeatedly before our eyes. We often see, on comparison with the normal fullness, appearances in which the collateral net decreases, and the plane elements increase at its expense. This is still further exaggerated in the pigment anomalies, for the separation of the pigment is only an *indirect* result of the circulatory changes, and pigment and the amount of blood in the skin do not completely correspond. Certainly the white spots always correspond at first, and for a considerable time in a remarkable degree, to the plane elements, and only with the disappearance of the whole anomaly does the pigment consumption reach the collateral net, so that the rete pigmentosum before it disappears becomes more and more delicate.

This form of primary pigmented neuro-syphilide is, under certain circumstances, and without the intermediation of any other syphilide, contemporaneous with secondary pigmented papular neuro-syphilides, so that by this also the common basis of a widespread syphilitic disease of the vessel nerve centres, in all pigmentary neuro-syphilides, is confirmed.

As I have not had the opportunity of examining a primary pigmented neuro-syphilitic macule, I give a short account of Bockhart's case, which, in my view, was distinctly a neuro-syphilide. Although, according to the unsupported statement of the patient, it developed on an ordinary syphilide, the form, configuration, and distribution of the spots all favour my view. Certainly many of the statements are only compatible with this view; the sudden appearance, the excessive duration of the pigmentation, and the slight development on the predilection areas of the ordinary syphilide (genitals, and waist above the umbilicus).

Bockhart found as important facts: thrombosis of long stretches of the sub-papillary vascular net and a swelling and multiplication of the nuclei of the adjacent endothelium. The tissue around these vessels was coloured yellow and contained free pigment, hæmatoidin crystals, pigmented leucocytes and connective tissue cells. And in the neighbourhood of certain unthrombosed capillaries, particularly in the papillae, were found wandering cells, without the endothelium presenting any change. The whole papillary body was dotted here and there with pigmented wandering cells. In the epidermis pigment was abundant, especially in the deeper layer, and inside the cells; the horny layer also was darker than usual. The pigment granules in the endothelium of the vessels Bockhart traces to broken-down red corpuscles; the amorphous and crystallised pigment masses in the neighbouring tissue, not to escaped blood corpuscles, but to blood colouring matter

escaped at the seat of the thromboi, the thrombosis to the endothelial change, and the pigmentation of the epidermis to the transportation of the cutis pigment by wandering cells.

The histology of the *diffuse pigmented neuro-syphilide* passing into the rete pigmentosum is naturally different according as one examines a pure neuro-syphilide or an embolised portion of skin, already the seat of roseola or papules. The following is the description of a case closely observed in my clinic, and the specimen was removed in such a way that there was in the middle a white plane element, of the colour of the normal skin of the breast, which first became visible fourteen days before excision, at the one end a dark coloured strand of the collateral net, and at the other, the edge of a large neighbouring, already desquamating roseola granulata, which was seated exactly on a strand of the collateral net. The greater part of the piece thus comprised the pure neuro-syphilide, only the one end its combination with roseola. All the sections gave the same results, which I will briefly sum up in the following points :—1. Most of the pigment was located at the ends of the section, and corresponded to the strand of the black net; it was less marked on the side of the roseola. 2. The middle part, corresponding to the white spot, was however by no means free from pigment, it is only less in amount and differently distributed. 3. The whole epidermis and the cutis beneath the superficial vascular net were completely free from pigment. 4. The pigment was present everywhere from the under margin of this net up to the sub-epithelial margin, in the form of equal, large, round, golden yellow granules in the lymph spaces of the cutis. 5. Its favourite seats were those lymph spaces which adjoined the perithelium of the blood vessels, and the hypertrophic spindle cells of the papillary body. 6. There was no pigment in the lymph spaces between the scanty plasma cells at the seat of the healing roseola granulata. 7. Not less interesting than the *presence of pigment on the whole surface* of the excised piece was the discovery of *vessel changes also over the whole surface* of the piece, without appreciable difference between the areas of the plane element and the collateral net. 8. These changes consisted in a swelling of the endothelia and perithelia of all the capillaries of the sub-papillary net and the papillary body, and in multiplication, most marked in the latter; further in an increase in volume in the spindle cells of the cutis. 9. At the seat of the white plane elements the pigment granules were distinctly less in number, and were scattered more singly and widely over the connective tissue cells, while their form and colour was the same as on the border of the section. 10. At the seat of the roseola granulata the changes described under 7. gave place to the ordinary ones of these eruptions, plasma cells appearing around the vessels;

the pigment here was less than on the opposite darkly coloured end but denser than in the middle. 11. Leucocytes either with or without pigment were entirely absent. 12. In the middle of the section it could be definitely established, by careful staining of all the connective tissue cell processes, that the scanty pigment granules were only *applied* to the cells, but on the ends of the section the possibility that the connective tissue cells closely surrounded by pigment, whose processes were mostly withdrawn, had not taken up pigment into their outer cell mantles, could not be excluded (clinical facts were not in favour of it, for it was gone in two months); the most of the pigment was certainly free in the lymph spaces.

From these facts I venture to conclude that in this form of pigment syphilis we have to do in the first place not only with a diffuse pigmentation, but at the same time with a diffuse cellular hyperplasia of the papillary body, which can be distinguished from the changes of single roseolæ or papules which may here and there be present; that further, the white spots develope from a disappearance of pigment, which on the primary and diffuse hyper-pigmented skin takes place at first only in relation to the plane elements, and only on the disappearance of the whole process, decolourises the whole collateral net; that finally this pigment consumption takes place in the papillary body in the pigment mostly lying free in the lymph spaces and surrounding the connective tissue cells, while the hyperplasia of the cells persists. That the more rapidly oxygenated plane elements should lose the pigment sooner than the more slowly nourished collateral net is readily understood. The essence of the whole manifestation lies, not in the net-formed depigmentation, but in the primary pigmentation and the cellular hyperplasia; a primary thrombosis I have not found as the cause.

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2. Prurigo Group.

Among the neurotic dermatoses there is a group of diseases which, in its severe itching and consequent scratching effects, in the formation of papules, vesicles, and crusts, and finally in epithelial hypertrophy and pigmentation, closely resembles certain eczemas, in particular, pruriginous eczema (which see). They are sometimes classed with these (as papular eczema) and sometimes experimentally separated. If we maintain parakeratosis as an essential symptom of the various forms of chronic eczema, these pruriginous diseases, in spite of the vesicles, belong no more to eczema than to the herpetic diseases. The primary flat epithelial affection, with the character of altered keratinization is altogether absent. The later widespread thickening of the epithelium and especially of the horny layer, which certain forms of prurigo share with certain eczemas, is a *secondary* phenomenon, induced by the severe pruritus and consequent scratching, and is common to several itching dermatoses.

More thorough clinical and histological examination indicates that the primary element, common to diseases of this group, is an *œdematous cellular nodule in the cutis*, through which they range themselves alongside the angio-neurotic dermatoses, the great cellular hyperplasia and the extraordinarily chronic character preventing them being included along with them. Added to this uniform element there are, in different forms, epithelial changes of different character, vesicles, pustules, epithelial necroses, and further, a general epithelial hypertrophy.

To these true pruriginous diseases belong at least the two following readily distinguishable forms—

(*a*). Prurigo mitis, Prurigo Willan.
(*b*). Prurigo gravis, Prurigo Hebra.

With Hebra I regard as "Prurigo" only those severely itching dermatoses which present primary nodules of peculiar character, while the name "pruritus" indicates every form of itching neurosis of the skin, which is not accompanied by a primary eruption. But according to this definition not only Hebra's prurigo is included, but also that of Willan, and possibly also still other forms—*e.g.*, many cases of Prurigo hiemalis Duhring, Lichen urticatus, &c. In contrast to Hebra's prurigo, which is a severe universal and long-standing disease, the group of the other slighter forms is not so uniform. The term, Prurigo mitis, which corresponds to Willan's definition comprises probably various types

which must be separated by further investigation. It is possible for me, from a long observation of three cases of Prurigo mitis, to present a pretty uniform anatomical description of the disease, and it is by no means, as has up to now usually been held, a mild variety of Hebra's prurigo.

(*a*). *Prurigo mitis, Prurigo Willan.*

In adults there appear in the thickness of the cutis, nodules, usually scattered, more rarely in groups. In size they vary from that of a peppercorn to that of a pea ; in colour they may be identical with that of the skin, white, or finally faintly reddened. They itch severely and are immediately scratched at their apices. They are found mostly on the extensor surfaces of the extremities, on the shoulders and hips, more rarely on the trunk and neck, and do not spare the flexor surfaces ; in some cases they are found most over large cutaneous veins and their points of division. The itching varies in degree, and only ceases when the papule is scratched and a dark scab occupies its apex. Through the coalescence of these eruptions, there develope more or less universal patches, and with continual remissions and exacerbations the disease may drag out its course for years, showing some unrecognisable dependence on the changes of the weather. The scratching may in time induce a moderate pigmentation of the skin, but it never goes on to the formation of a weeping crusted surface. This last character differentiates it from pruriginous eczema, as does the absence of epidermic thickening from the prurigo of Hebra. Although the disease may last for years, the skin remains soft and the panniculus is retained. There are frequently disturbances of the circulation of the skin, especially on the extremities; anæmia or cyanosis.

Among the most recently developed papules of prurigo mitis some are found of very simple construction. Epidermis and papillary body are, as in every acute swelling "in vivo," much folded, but otherwise scarcely changed. There is no proliferation of the epithelium, nor any suggestion of parakeratosis. But the lymphatics of the whole cutis are dilated, and the adventitia of the vessels is abnormally cellular, so that they appear as thickened vascular cords. The scattered connective tissue cells are also increased in number and size. Mast cells, collagenous and elastic fibres and muscles are normal. The hypertrophy of the connective tissue cells never goes on to the formation of plasma cells, nor is there any increased emigration of leucocytes. The chief changes are hypertrophy around the vessels and œdema of the cutis. These symptoms are more evident as one reaches the middle of the papule, and diminish in intensity towards the periphery. In the central sections there are usually some papillæ rich in connective tissue cells and somewhat œdematous. And here is found also the single recognisable epithelial change, which consists in a thickening of the horny layer, which is sometimes split into lamellæ.

More characteristic appearances than in these recent papules are found in older ones. Quite characteristic changes are found inside the

prickle cell layer. Usually above some œdematous and abnormally cellular papillæ the regular mosaic arrangement of the epithelium is spoiled by rounded areas of four, eight to twenty and more cells. These are solid, they form no vesicle, but as their volume is not inappreciably increased, the adjacent epithelia, yielding to the pressure, arrange themselves tangentially around the area. While the protoplasm of the surrounding cells is normal and the interspinal canals more definite, owing to a slight œdema of the epidermis, the cells in these areas have their protoplasm swollen and cloudy, the cell margins are blurred and the nuclei, from the pressure of the protoplasm, are partly converted into small rods. Further, there are in the same areas, at most, a few leucocytes; their presence is not constant.

These areas arising from cellular swelling are found preferentially in the middle part of the prickle layer, more rarely in the superficial or basal parts. In the latter case the ball of swollen epithelium may separate itself entirely from the prickle layer, and, like a sequestrum, remain lying between it and the papillary body. In many cases the horny layer passes unchanged over these areas of the prickle layer, but, sometimes it descends deeper, is locally stretched and deficient in the granular layer. Small areas unite to form larger ones, and the cell bodies run together to an always more uniform cloudy mass, taking an acid stain. The nuclei retained in this gradually lose their staining reaction, and finally there remains a mass of epithelial debris, with a few well-preserved leucocytic nuclei. But it is remarkable that the areas, even when degenerated, retain their rounded or ovally stretched form, without undergoing liquefaction. At this stage the surroundings of the areas share also in the change, the epithelial cells for a certain distance are swollen, and the inter-cellular spaces widened, but it is only rarely that there is a running together of adjacent cells and then a peripheral extension of the necrotic areas.

If attention is once drawn to these necrotic softening areas, an examination of one's preparations, directed to this end, will disclose a number of slighter and earlier changes in the prickle layer, evidently of the same nature. These are of course best observed if protoplasm stains be used. We find then small lighter places in the prickle layer, in which either the inter-cellular spaces or the nuclear cavities over a certain area are much dilated, or we observe scattered epithelial cells of greater extent and less staining capacity, with their protoplasm spottily clouded, or finally only a few nuclei much swollen and faintly stained. One always notes at the seat of these minimal pathological changes, a somewhat irregular arrangement of the epithelia.

Corresponding to these irregularly lying softening areas of the epithelium, the papillary body is also affected at different points, in different intensity, and usually the changes on both sides correspond.

Some papillæ are only œdematous, others exceptionally rich in leucocytes. At such places leucocytes are found around the capillary system, which is in general more cellular than in the slighter forms of the affection. But in general the leucocytic migration is slight. Between the swelling papillæ the epithelial ridges are small and often shortened; epithelial mitoses are never found, and the punctiform thickenings of the prickle layer are to be ascribed to the enclosure of the swelled areas and the surrounding œdema.

The cutis is, apart from the inflammatory symptoms of the papillary body, in general little changed. The œdema and the cellular infiltration of the vessel sheaths extends from the upper and middle part of the nodule, in diminishing degree downwards and to the sides.

Where the papule is scratched, one finds over its centre the horny layer torn, covered by a bloody crust, and the place of an underlying necrobiotic area occupied by a bloody fluid.

Prurigo mitis is therefore, an inflammatory process, which leads in the cutis to inflammatory proliferation and spastic œdema, and in the epidermis to scattered areas of softening, the latter being apparently the cause of the itching. To an eczema papule this prurigo papule has not the remotest resemblance.

(*b*). *Prurigo gravis, Prurigo Hebra.*

An affection equally obstinate as the previous one, but which, from its commencement in early youth, leads to much severer disturbance of the skin. It begins, usually as the lichen urticatus of Willan; but later the urticarial factor becomes less, while the inflammatory disturbances remain and constantly increase. It leads to hardening and thickening, especially on the extensor surfaces of the extremities, less on the skin of the trunk or face, and never on the flexures of the joints. Further, there develope pigmentation, excoriations, impetigines, furuncles, and other effects of scratching, and finally hypertrophy of the epidermis and disappearance of the panniculus of the affected parts. The disease shows exacerbations, usually in winter, in which, accompanied by the most severe itching, small, whitish, deep-lying nodules appear, scattered over the affected portion of skin, and are immediately scratched. The adjacent lymphatic glands, especially the inguinal, are early affected and become very much swollen.

In the histological examination of prurigo gravis it is especially important definitely to establish the character of the primary nodular elements, which are only from time to time evident among the much more striking secondary changes. These last closely resemble those found in severely itching eczemas of long duration. Thus I have examined a series of very severe long-standing seborrhœic eczemas, which, in relation to the pigmentation, thickening of the epidermis, tight fixation of the fatless cutis and excessive itching on the extremities, closely resemble the severest prurigos, but which, from their relatively

late commencement and their history, as well as from the extension of the affection to the flexures of the joints, were recognisable as eczemas of definite variety. For the histological appearance of this variety see under "results of eczema."

The primary nodules of Prurigo gravis have given origin to a prolonged and still unfinished controversy, in relation to their development and histological structure. If we leave out of account the older vague ideas, there remain three different views. The nodules may either be pseudo-papules, depending on the contraction of the arrectors (Auspitz), or spastic œdematous papules of the cutis, closely allied to urticaria (Riehl), or epithelial papules due to acanthosis (Caspary). It is evident that such grossly contradictory views are only to be explained by the fact that the authors had before them entirely different things. My investigations, mostly carried out on a case of slight but typical Hebra's prurigo in a young man from the Russian frontier provinces, who was long under observation, indicate indeed that each of these different views contains a modicum of truth. The most important element, however, appears to me not to have been noted by these authors, but more recently by Leloir and Tavernier, who describe a degeneration of the prickle cells with consequent cavity formation; possibly also Kromayer had before him in his "exudation cysts" encapsuled vesicles between the horny lamellæ.

There lie before me from this case nine successively removed, mostly fresh nodules, which fully indicate the multiformity of the primary prurigo nodule. They were always developed with great itching, on skin previously free from nodules, sometimes pale and sometimes of an inflammatory red colour; a few had at their apices a lanugo hair, but the majority not; in several the summit was occupied by a drop of pus, and was somewhat transparent. To these preparations were added two, which Dr Lukasiewicz, with the friendly connivance of Professor Kaposi, extirpated for me in Vienna hospital, and which, in the confirmation of the Hamburg results, are naturally most valuable. Of these eleven primary papules, removed from three different patients, four showed at their apices pustules, three, in their centre lanugo hair follicles, two, tiny vesicles, evident only under the microscope, while two were simple urticarial papules without any evidence of change in epidermis or hair follicles.

Common to all without exception, is the double phenomenon of a spastic œdema of the cutis and a very marked increase in number and size of the perithelia of the vessels. This latter is in most of the papules much more developed than in Prurigo mitis, but here also does not lead to the formation of plasma cells. In some papules the vessel cords are almost as thick as in young neuro-leprides.

So far Riehl is perfectly right; every prurigo papule has an urticaria-like basis. But on the one hand there is added the proliferative inflammation of the vessel sheaths, and on the other still more characteristic changes in the epidermis. The earliest changes in this connection were found in two papules, where, in the centre of the spot, in an area of the diameter of two papillæ, the prickle layer, with the exception of a few remains, is degenerated to a pulpy mass. These small cavities are covered by a much thickened horny layer, split on its under surface, and from beneath there reach into it the few papillæ, swollen and œdematous. Beneath this vesicle, developed from the primary softening and necrosis of the prickle cells, which was macroscopically invisible, there stretches a small zone of marked cellular infiltration of the papillary body and the upper layers of the cutis. Four other papules, reddened and evidently irritated by scratching, show the transformation of this vesicle into an impetigo pustule, which is, however, in many ways different from the ordinary staphylogenic impetigo. For the attracted leucocytes do not here fill a self-made, elliptical space between horny and prickle layer, but penetrate into a pre-existing, sharply rounded cavity, formed by the destruction of the prickle cells, its upper narrow end on the split up horny layer, its lower broader one on the almost epithelium-free papillary body. As a result of this—secondly—the form of the impetigo is not semi-spherical, but remains more or less conical, even when it has increased very much in breadth compared to the vesicle; consequently it is not evident macroscopically as a drop on the skin, but is embedded in it, and only its apex shimmers through as a yellow point. But most important of all is the fact that this impetigo contains no staphylo-cocci. But I was able to find on preparations stained with methyl blue and decolourised with glycerine ether, on the under surface of the horny layer and directly over the centre of the drop of pus, a number of transitional epithelial cells transformed into shining flakes having no nuclei and not staining, and these were beset with very minute cocci, singly or in pairs. They were distinguished from nuclear degeneration products by their regular contour and equal size. They did not resist iodine, and consequently were not demonstrable by Weigert's method. In addition there were a few, lying between the adjacent horny cells over the centre of the drop of pus.

These vesicles are evidently the same as Leloir found, and in them he added a most important fact to those already known of prurigo. They form a remarkable analogy to those epithelial changes which distinguish prurigo mitis, and which, in spite of their multiformity, come into the category of primary softening and consequent necrosis of the

epithelia. Unlike Leloir I could not determine any connection between the vesicles and the sweat pores.

But those authors who lay stress on changes in the hair follicles are to a certain degree correct. For one certainly finds the arrector of some of the follicles thickened and persisting in spastic contraction, so that the hair follicle is erected and the point of insertion of the muscle in the papillary body appears funnel-shaped. This observation would corroborate the view of Auspitz that the prurigo nodules owe their origin solely to a contraction of the arrectors, did not the same hair follicle show proliferative and exudative inflammatory changes and necrosis, and thus relegate the contraction and increased size of the skin muscles to an accompanying or secondary symptom. We find in all the hair follicles which occupy the centre of a prurigo papule (three out of eleven cases) the prickle layer thickened, and even that part next the surface, although in lesser degree, in a state of proliferation. If the observations of Caspary as to epithelial proliferation are to be met with constantly anywhere it is in the follicle itself and in its immediate neighbourhood. It resembles those acanthoses, which are to be found in the neck of the follicle and its neighbourhood in certain infectious diseases of the epidermis, where infectious germs have entered into the neck, and the more, as here the epithelial proliferation is more marked in the upper third of the follicle. In addition to the acanthosis we find also the above-mentioned formation of vesicles, with softening of the prickle layer and subsequent leucocytosis on the surface, then of the follicle, and in analogous fashion on the upper section of the follicle. Indeed, one of the papules shows a widespread necrotic softening and vesicle formation in the epithelium of the follicle, so that the hair swims free in the first hypertrophied and later liquefied region of the prickle layer. In this case the leucocytosis is absent, and the walls of the blister consist of necrotic basal cells of the prickle layer of the follicle, an indication that the softening and necrosis are not dependent on the immigration of leucocytes, but are primary changes.

It cannot be denied that all these changes in the epidermis of the surface and the follicles point to a parasitic development, and it certainly appears possible that the organism causing the epithelial necrosis stands in the closest connection with the etiology of the whole disease, but that it does not induce such striking phenomena in the epidermis in all cases. Were this hypothesis to prove true, prurigo would have to be removed from the neurotic dermatoses and classed with the infectious inflammations of the epidermis.

If we bring together these various facts, we have in the primary papule of prurigo gravis, on the basis of a perithelial growth of a chronic character and an additional acute spastic œdema, a series of different epithelial changes of the surface and the follicles, above a central

severe cellular infiltration of the cutis. These epithelial changes consist in a circumscribed growth of the mouth of the follicle and its immediate neighbourhood, and in circumscribed areas of softening and necrobiosis of the epithelia, which, perhaps spontaneously, but more certainly after scratching, take on the character of impetigines.

In long-standing prurigo Hebra, there appear regularly diffuse deep-reaching alterations in the whole structure of the skin, which, taken altogether, enable one to diagnose it at a glance even when—as is often the case—the primary nodule is not visible. The skin of the whole body is very anæmic, pigmented, dry, deficient in fat, tightly stretched on the extremities, on the extensor surfaces of which the epidermis is greatly thickened, coarsely creased and covered with scratch marks, especially with scratched papular spots. On the flexures of the joints and on the flexor surfaces generally, the pathological process ceases somewhat suddenly, although the chains of glands, especially the inguinal ones, are swollen. A constant itching, especially on the extensor surfaces, a tendency to urticarial eruption, and the patchy appearance of the characteristic pale or rosy red prurigo nodules, complete the picture. As these clinical phenomena would lead us to expect, most of the histological changes are in relation to the epidermis. The cutis shows—in contrast to the fresh papule—over all a cellular infiltration of the vessel sheaths even in the deepest layer, but it is not pronounced. Leucocytes are only found at the seat of fresh eruptions. The lymph spaces are dilated, but, corresponding to the increased vascular tone of the prurigo skin, the blood-vessels are not. The papillary body, which is irregularly swollen and œdematous in the acute eruptions, is reduced to the normal, or even below it, as the gradual universal epithelial growth thins the papillæ, and in some places completely flattens the papillary body. The prickle layer has become thickened, but so slowly that mitoses are very rarely met with. The granular layer is normal; the horny layer, on the other hand, is still more thickened, and many of its fine furrows are obliterated, so that the creasing of the epidermis is limited to the deeper furrows, and is thus abnormally coarse. The diminution of the furrows of the epidermis indicate both an abnormal firmness and hardness of the horny layer, and both the thickening and the increased hardness of the horny layer induce the leathery firmness, the tension and the pachydermatosis of the skin, and, through pressure on the underlying structure, the disappearance of the panniculus.

As we see, this histological appearance closely resembles that of eczema which has become pruriginous (which see). The acanthosis and hyperkeratosis, induced by vascular hypertone, anæmia, and constant itching, and kept up by permanent scratching, is common to both processes. But it is not difficult, by the recognition of parakeratosis

and more marked epithelial growth or distinct eczematous appearances, to distinguish eczema pruriginosum from Prurigo gravis.

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3. Hydroa Group.

(Dermatitis herpetiformis Duhring.)

By hydroa I understand a chronic nervous affection of the skin, not greatly influencing the general condition, which, after varying intervals of freedom, leads to regularly recurring, more or less universal eruptions, accompanied by burning and itching, which show many varieties of an erythemato-bullous main type.

On account of the great individual peculiarities of each type it is difficult, if not impossible, to present a uniform clinical picture. We may, however, recognise severe universal and slighter, more localised cases; the former are usually confounded with pemphigus, the latter with eczema. Etiologically two smaller groups may be separated: Hydroa gravidarum and Hydroa puerorum. These cases are usually benign.

(*a*). *Hydroa mitis.*

My material comes from a typical case of the more localised benign form. There appeared, mainly in the arms and legs, more rarely on the head and trunk of a middle-aged lady, spots or papules, the size of a peppercorn to a pea, which developed into vesicles or bullæ, they were sometimes isolated, sometimes in large groups, when they were gradually surrounded by a firm infiltrated red halo. They caused intolerable itching.

Two just developed papules showed at the apex, one of them a scale, the other a single vesicle. The most marked symptom is a pronounced cellular infiltration and œdema of the papillary body, along with purely passive changes of the epithelium. The cells in the papillary body are solely connective tissue cells of flat or spindle form; there are found neither any considerable number of leucocytes nor cubical plasma cells.

The collagenous tissue of the papillary body is swollen, its lymph spaces are dilated. The heads of the papillæ are especially œdematous, and between them the epithelial ridges are compressed and elongated. In the centre of the papule the swollen and cellularly infiltrated papillæ sometimes run together to large, round protuberances and swellings, over which the epithelium is stretched, thinned, and converted into a scale. Close beside these very œdematous central papillæ we see, in

many sections, thicker, broader epithelial processes running downwards. But their increase is not induced by cellular proliferation, for no mitoses are recognisable, but by serous swelling of all the prickle cells and by marked dilatation of all the lymph spaces between them. In this sodden epithelium there appear, at the most different times and places, very different vesicles. In both the fresh papules the smallest vesicles are found in the horny layer, which covers the centre of the papule. The macroscopically visible vesicle in the centre of one of the papules is seated in the middle of the prickle layer, and is mainly formed by the dilatation of the inter-epithelial lymph spaces, for the space contains compressed but not swollen epithelia. There is never here any reticular degeneration of the individual œdematous epithelia, though it is later sometimes evident at the periphery of the larger bullæ.

Six other older spots, from the same case, agree in showing an extension of the process in this direction, that the cellular infiltration of the papillary body constantly increases in amount, but is always limited to the surface of the cutis between the papillary body and the superficial vascular net. Only on the vessels which correspond to the spot does the cellular infiltration and adventitial œdema extend and the vessel sheaths are thickened, cellular, and swollen. Even if the papule lasts long, the cutis proper only shows a trivial increase in cells and a slight œdema. On these more persistent papules of the benign localised cases it is especially clear that the common basis of all the eruptions is an œdema and a hyperplasia of the cells and inter-cellular substance of one single vessel, and its distribution in the papillary body. The more recent papules are only distinguished from each other, that in some the cellular infiltration of the papillæ, in others the œdema predominates; in the latter case they form club-like swellings of glassy, transparent appearance. In the older papules both the cellularity and the œdema are less, compared to the new formation of fibrillary tissue in the papilla, and we thus understand the extraordinary resistance and obstinacy which such older papules show.

To these main facts, the epithelial changes play only a secondary rôle, although the clinical appearances, often so different, are generally caused by epithelial changes. This involves no contradiction; on the contrary the clinical appearance of the eruption could not be so polymorphous, if any definite epithelial change, such as the formation of bullæ, were found in every case.

The only characteristic and always recognisable factor is the basis of the bullous formation, the œdema of the epithelium.

The results of the œdema are on the older longer existing papules very varied. The œdematous horny layer becomes a scale, without

any keratohyalin; this is thrown off and the sodden epithelium dries up into a scab, which comprises almost the whole *supra* papillary prickle layer; underneath the scale small elementary *inter*-epithelial vesicles are formed from the dilated lymph spaces, which run together to form larger ones; here and there this process reaches the developement of larger bullæ, which extend rapidly from the transitional layer towards the *basal* epithelial layer, among the prickle cells, compressing them and drawing them out to long bands. The fully-formed blisters are always surrounded by a firm, compressed epithelium, and are filled with fine, granular fibrin, among which wandering cells slowly appear, but not in particular numbers (unless there is secondary suppuration). In the older blisters there are found, especially near their covering, collections of softened epithelium, showing the commencement of reticular degeneration with the formation of intra-epithelial vesicles. But this latter is not part of the typical appearance of the disease. The older and firmer the papules become, the more limited is the formation of blisters; there exists then only formation of scales, an œdematous swelling of the prickle cells and a dilatation of the inter-epithelial lymph spaces. But even then, the passive character of the epithelial changes may be recognised from three further symptoms: the absence of mitosis of the epithelium, the lesser development of a super-papillary prickle layer, and the lanky, thin character of the inter-papillary network of processes.

(*b*). *Hydroa gravis.*

The material came from a severe case, continually recurring with slight intervals for years. The pruritus was very well marked, and nutrition thus gradually diminished. The blisters appeared suddenly on almost all parts of the body without exception, and on apparently normal or slightly reddened skin, sometimes in the middle of an eruption of figured erythema. They had thick walls, and were of the size of a pepper-corn up to a linseed, seldom larger, but often *flattened;* they were filled with clear yellow, never purulent serum, they healed with remarkable rapidity, and left behind them slightly infiltrated pigmented spots, which only gradually disappeared.

Three blisters excised, after lasting for different times, show, in contrast to the small vesicles of hydroa mitis, a remarkable agreement in their histological appearance.

The whole epidermis at the seat of the blister is raised as a whole from the papillary body, and runs over the blister as a covering. The blister corresponds only to the centre of the inflamed papule, which here also consists of the wide-spread œdematous swelling and cellular infiltration of the papillary body. On both sides of the blister

the papillæ are spherically swollen, and the epithelial processes between them are thinned. Close to the vesicular elevation, one sees on certain places a loosening between the epithelium and papillary body, which prepares the way for complete separation. This loosening is as complete as that which it is possible to induce on the corpse by means of acetic-acid or vinegar. Here, as there, the swelling of the papillary body is the chief factor leading to the loosening. The papillæ, stripped of their coverings, reach with their spherically swollen apices naked into the wide cavity filled with serum and fibrin. The elevated epithelium still shows all the epithelial processes and the markings of the papillæ, though they may be somewhat thinned by stretching and pressure. One or two ducts of the coil glands stretch through the blister and are somewhat drawn out of the cutis, without being torn. The cellular infiltration is, in the rapidly appearing and rapidly healing blisters of these cases, much less than in the more considerable papules of hydroa mitis, though the form and distribution of the cells is the same. Here also we have ordinary connective tissue cells, flat or spindle shaped, and here also all migration of leucocytes is absent, at least at the commencement of the process. The growth of cells is again limited to the vessel trunk and its papillary distribution; the papillæ are the parts most infiltrated by cells.

The older blisters differ from the younger, both in the marked predominance of the papillary infiltration, and through secondary changes in the blister and its surroundings. In the contents of the blister, firm fibrinous coagulation takes place, and further transudation increases the pressure in them, and flattens both the epithelial processes of the cover of the blister and the papillæ at its base, so that it needs considerable attention in order to recognise, in the remaining folds and projections, the previous structure of the part. At the side of the blister the œdema leads to the softening of certain sections of the epithelium. Those at the edge of the blister usually run together, as do the epithelial processes, elevated from their furrows. Inside the elevated and distended covering of the blister, the compressed epithelial cells swell up again somewhat, become clear, their nuclei less stainable, and finally they soften into small colliquative vesicles. All around the blister the epithelial lymphatics are dilated, but relatively free from wandering cells. The epithelial cells show no mitoses, and the rapid healing is therefore somewhat remarkable, unless it takes place through the simple replantation of the elevated epithelium on the base of the blister. Such a course would not be impossible, for, except for the œdema, almost all the epithelial degenerations, which usually accompany blisters, are absent. When secondary suppuration is added the healing process is much slower.

What is here described of these two cases of hydroa corresponds well to the possible extremes of the disease; on the one hand, multiple formation of small vesicles at different heights of the epidermis, on the other, violent elevation of the whole epidermis from the papillary body. But many cases of hydroa must be ranked somewhere between these extremes. Two preparations from two American cases, for which I thank Dr Elliot, correspond in histological relation, exactly with my two cases, the acute one to my benign, the chronic to my case of hydroa gravis. In the latter there is a slight suppuration in the blister, which is, according to my clinical observations, somewhat uncommon.

The histological basis of the affection is, however, though at the first glance the pictures appear so different, one and the same; *the œdema and cellular infiltration corresponding to a vaseular area of the skin, whose ehief seat is the papillary body, the utterly passive behaviour of the epithelium, whieh only presents œdema and inter-epithelial blisters, or is eompletely elevated by serum, and finally the eomplete absenee of leueocytosis.* That in one series of cases, the serous transudation leads to swelling of the epithelium, and in another to elevation of the epithelium, must depend on a diminished firmness in the union between epithelium and papillary body in this latter case. In it the same vessel nerve irritant, which in better constituted skins only leads to serous inflammation at certain areas, leads here to elevation of the epithelium, and thus these cases become severe and universal. This more expansive action appears on the other hand to have the meaning for the single spots, that the inflammatory appearances in the cutis are more rapidly recovered from, than in the localised form.

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4. Herpes Group.

(H. genitalis. H. facialis.)

In the neighbourhood of the genitals, or the mouth, with or without other diseases of the genitals or the digestive tract, there appear, accompanied by burning sensations, rapidly developed, separately placed groups of vesicles, the size of a mustard seed, filled with clear yellow serum: they are seated on a *common*, usually much reddened, always œdematous swollen base. The vesicles dry up after a short existence into brown crusts, and fall off in about a week without

leaving scars, or they develope into polycyclical margined ulcers. In distinction to Zoster one attack predisposes to others, and bilateral attacks are commoner than in Zoster.

Considering the frequency of the affection, I have relatively little material, three cases of Herp. genitalis, excised from the living, and a piece of skin with several spots of herpes facialis from the corpse. As in acne, the innocent nature of the affection, which is known to the patient, makes the obtaining of material from the living difficult, and I would therefore the more closely direct attention to the interesting and most promising study of herpetic eruptions.

Only one of the excised herpetes genitales concerns a fresh spot still presenting the vesicular character, another shows the drying up and exfoliation of the vesicle, while the third shows the transformation into a herpetic ulcer.

The herpetic vesicle was situated towards the side of the group, and was particularly large and well developed. The sections showed a flat, large, thick-walled blister, whose cavity was almost entirely subepithelial. It has arisen from elevation of the much-altered prickle layer from the swollen papillary body; only a few complexes of prickle cells are still adherent in the inter-papillary furrows of the latter. The thick cover showed peculiar steps and stairs. There follows on a pretty thick horny layer a (upper) zone consisting of six or eight rows of cells, which at the side of the blister passes directly into the granular layer and most superficial prickle layers of the neighbouring epidermis, and has evidently arisen from swelling and degeneration of these cell layers. The cells are increased in size, their contour and their prickles are well preserved, but they are much degenerated. With the methyl blue orcein method they take up no methyl blue and only very little orcein, and it is evident that almost all the nuclei, with the exception of atrophying remains, are washed out of them, but the nuclear cavities do not fall in. The explanation of this peculiar appearance is furnished by fibrin staining, for the whole zone takes up the fibrin colour strongly, it is, then, fibrinously coagulated, and thus the prickles and the wide lymph spaces stand out sharply between the dead epithelial cells. In these inter-epithelial lymph spaces there may be found a few long drawn out leucocytic nuclei, normally stained. The superficial layer of prickle cells in the neighbourhood, into which the necrotic zone of the cover of the blister passes, are acidophilic, they take, with this stain, the orcein.

We have here to do with a true coagulation necrosis of the upper prickle layer; without having lost their lateral connections, these epithelial cells have become necrotic; the protoplasm has given up its normal staining capacity, and by taking up fibrinogenous substance

from the fluid surrounding it, has undergone a transformation into a truly fibrinous coagulated mass. By the same factors, death and saturation, the nuclei of this zone are washed out of the well-preserved mummies of the cell bodies. If anywhere, in regard to epithelium, the name "coagulation death," in the sense of Cohnheim, may here be used, and if anywhere an example illustrates the near relation of the washing out of the nuclein substance on the one hand and the formation of fibrinoid substance from the cell body on the other, in coagulation necrosis, in the sense of Weigert, this is it. And a greater contrast than between these coagulation-necrotic cells of the upper prickle layer and the ballooned young epithelia in zoster and in small-pox, can hardly be conceived. There, the fibrinoid coagulation of the cell scaffolding with retention of connection and solution of the nuclei, here, the isolation of the also fibrinously coagulated cells through the complete loss of the prickles along with good nuclear staining and marked amitotic nuclear constriction.

The coagulation necrotic zone is margined below by a layer of flattened cells, thinned in the centre, but otherwise normal and staining normally, which, before the elevation of the cover of the blister, formed part of the middle layer and lower prickle sheath. The existence of this second almost normal layer indicates that the primary epithelial changes, before the formation of the larger blister, affect, not the whole, but only the upper subcorneal prickle layer, and further that the elevation of the whole epithelium is a secondary occurrence; for were it the primary appearance it would be incomprehensible why only an isolated part of the cover of the vesicle should degenerate in so definite and characteristic a way.

Further down, following the layer of normal epithelial cells, come necrotic ones which pass into the necrotic cell debris which, along with a thick fibrin net, fills the not much elevated sub-epithelial cavity of the blister. Most of these cells show, instead of the nucleus, a cavity, and some of them form rounded fragments, others irregularly twisted bands. There is no increase in the nuclei; the cell substance stains less (acidophil) than that of ballooned epithelium and in certain places is completely dissolved in the fluid of the blister. And thus these undermost cells of the covering, as well as those immediately next the epithelial debris in the cavity, are to be considered as coagulation necrotic. In the latter one finds a moderate number of polynuclear leucocytes which, in regard to their protoplasm, show a similar metamorphosis as the epithelial cells, while the nuclei last longer and stain better than the epithelial nuclei. The epithelial debris consists chiefly of the epithelial ridges which are not completely loosened from the interpapillary furrows and here and there unite the cover and the base of

the blister. The heads of the papillæ, on the other hand, which are globularly swollen, reach into the cavity of the blister, are completely stripped of epithelium, and to them correspond usually the normal, simply stretched epithelia of the covering.

The fibrinous net in the cavity is pretty regularly small meshed and consists of granular threads.

In the neighbourhood of the vesicle the prickle layer is as a whole widened, and in its upper part it is œdematously swollen; the *basal* parts of the prickle layer are here and there elevated over the papillæ by a fibrinous exudation, while the parts corresponding to the ridges are *laterally* compressed and adhere to the cutis.

If one glances over the whole process of vesicle formation, as here indicated, on a typical herpetic vesicle, we have to do with a fibrinous inflammation of the epidermis, which runs in two ways or directions. The primary change affects the older, superficially lying prickle cells, and converts them into an anuclear fibrinoid degenerated, coagulation necrotic layer. At the same time the epidermis loosens as a whole from the swollen papillæ, and, as the exudation advances, there developes a sub-epithelial blister, whose covering is formed from layers of necrotic or simply stretched prickle layer, and whose walls and contents again undergo coagulation necrosis.

Future investigation will have to determine, whether the formation of vesicles in herpes genitalis always takes place thus, or whether the definite separation, existing here, into sub-corneal, inter-cellular œdema spaces and a sub-epithelial vesicle is only caused by the great thickness of the epidermis on this particular place. Clinical observation indeed is in favour of the presence of very superficial (sub-corneal) and deeper (sub-epithelial) vesicles, of which only the former rapidly dry up. In the space between this vesicle and the neighbouring vesicles of the group, the epidermis is as a whole thickened, the cells are increased in size, partly œdematous, and the inter-cellular spaces are widened. Here and there the epithelium is loosened from its support. One meets a few mitoses in the basal prickle layer, and a few leucocytes.

Both under the vesicle and under its surroundings, thus in the whole regions of the herpetic eruption, the cutis is in its whole thickness œdematous. The blood vessels are markedly dilated, but the lymph vessels relatively more so. All the blood vessels show a general, not very marked migration of leucocytes and—as is very well to be distinguished with good protoplasm staining—a collection of closely-packed small cubical or larger, roundish connective tissue cells. These remind one in their form and arrangement of plasma cells, but they contain only little granular, on the contrary, more spongy protoplasm. Possibly the great œdema of the skin hinders the formation of proper

plasma cells. The spindle cells of the rest of the skin are throughout enlarged, the mast cells, roundish and faintly stained.

My second case is that of a whole group of already dried-up herpes, and shows on every section several vesicles in this stage; most of them are distinctly smaller than in the case just described, that is, they correspond to an area of the diameter of two to three papillæ. The cutis shows here, both under the vesicles and in the intervals, great œdema, opening out of the lymph spaces, dilatation of the lymph and blood vessels, and formation of small cellular areas, of the character already described, in their immediate neighbourhood. But what has made great progress and gives to the sections at the first glance a completely altered appearance, is the migration of leucocytes. This takes place in moderate degree from all the blood vessels, but reaches its climax in relation to the papillary loop under the vesicle. Here the wandering cells collect from all sides in such masses that the papillæ, or at least the apices of the papillæ, show only closely packed leucocytic nuclei and the rest of their structure is completely obliterated. Where the epidermis is loosened over the papillæ, and a sub-epithelial vesicle thus developed, the cavity is filled with leucocytes and these permeate in large quantities the crust lying upon them.

This crust presents in all cases, even if no elevation of the whole epithelium has taken place, two definite layers. The most superficial consists of the old horny layer and the contents of the primary vesicle, coagulated into a crust. In this one can, by appropriate staining, still recognise the epithelial nuclei, which are pressed asunder by coagulated exudation and leucocytes. The deeper layer consists of the now flattened and (parakeratotically) cornified cells of the previous deep prickle layer, and is permeated by great quantities of leucocytes.

While some vesicles show only very nuclear fibrinous crusts over a cellularly infiltrated and swollen papillary body, one sees in other cases both parts separated by a space filled with leucocytes, a sub-epithelial vesicle. Whether in the former case there is no elevation of the epidermis, or whether after the passage of the leucocytes its lower layers again approach the papillary body, must be left undecided. At all events these observations of the second stage correspond well with the above-given description of a fresh vesicle.

Here also we have to do with a fibrinous inflammation of the cutis and epidermis, which reaches into the depths further than any simple epidermic affection of the same gravity, in general, does. Here also the leucocytosis is, from the commencement, wide spread, and now, towards the end of the process, dominates the field. The other secondary simultaneous products of the disease, the crusts, point also here, not to a colliquative degeneration of the epithelium, but to the formation of a simple super-

ficial, or a superficial and a second deep-seated pressure vesicle, which is first filled with fibrin and then with leucocytes. By this filling with exudation the accompanying processes of degeneration of the dilated epithelium (coagulation necrosis) are here no longer recognisable.

The third of my cases fits in exactly with the second. Only here, the rapid encapsulation of the vesicle and crust by cornified epithelium does not take place, but there is more deeply extending destruction.

The crust and the papillary body, both converted by a great migration of leucocytes into a uniform nuclear layer, in which the margin between epithelium and connective tissue is difficult to recognise, are elevated from the side as a whole, and exactly where the leucocytosis marks off, in almost a straight line, the underlying, relatively normal skin. After elimination of this layer there remains a flat, sharply cut out ulcer, which is not capable of simple cornification, and therefore, of rapid healing.

The changes of the cutis are in this case exactly the same as just described. It may be noted that in all, the elastic substance in the lower part of the cutis has disappeared, except for small remains, which, in view of the severe inflammatory œdema, is not surprising.

The single case of H. facialis which I had the opportunity of examining was from the corpse of a patient, who died from a febrile disease; it affected an ala of the nose and a part of the upper lip. The vesicles here were mostly healed, and in their place were thick fibrinous crusts, seated on the distinctly thinned and somewhat œdematous prickle layer. The epidermis between the vesicles showed in its upper part, here and there, œdematous separation of the prickle cells, in its under part, mitosis. The crusts contain few leucocytes but a considerable development of saprophytes of the most varied kinds. The cutis is still a little œdematous, and around the blood-vessels are cellular areas of the characters described above. The elastic tissue is relatively well preserved. The subject is much in need of investigation.

Zoster.

After more or less pronounced prodromal neuralgia affecting unilateral nerve regions, there appear suddenly, in relation to this, lenticular *groups* of painful papules, *surrounded by red halos.* They appear *in patches* on the trunk in the form of a half girdle, always *separated by healthy areas of skin*, are usually *monolocular*, but *several of a group run together;* more rarely they are arrested at the papular stage. Now and then the vesicles become purulent or hæmorrhagic and then break down readily; very rarely they are from the commencement replaced by grouped miliary necrosis; in this case scars are formed. After the disappearance of the cutaneous disease, there remain neuralgias, paralyses, atrophies, and other nerve disturbances. The individual groups of vesicles have a cyclical course of one or at most two weeks, according to the extent of their development, the whole dermatosis lasts from two to four weeks. Its

severity is by no means concomitant with that of the nerve affection, and this cannot be looked upon as a sufficient cause of the skin disease. Both are rather co-effects of the same acute, often epidemically appearing infection (Pfeiffer). According to this author the localisation of the groups of vesicles indicates their origin from arterial embolisms, but this needs further investigation. In favour of its infectious nature are the immunity which an attack confers and the histological appearances.

The vesicle of Zoster has a structure very unlike that of most other vesicles. There is in it a particular form of epithelial degeneration, in its most perfect development, which is present, though in less degree, in other processes (Varicella, Variola), and this definitely affects the appearance of the vesicle. Where in other cases the process of colliquation converts the prickle layer into a system of cavities, vacuoles appear in the œdematous much enlarged epithelial cells, and the cells then present a meshwork of small cavities and larger ones arising from confluence (reticulating degeneration). In Zoster, on the contrary, all the cells affected by colliquation preserve their contour, even their size. But they lose their prickles, and thus their connecting bridges fall apart, and they lie for the most part free and loosely heaped one on another at the base of the blister. But further they lose also their protoplasmic character and their consistence, they become opaque, take the fibrin stain, and, continuing to swell, are converted, through pressure and traction, into the most varied and extraordinary forms. With suitable staining one may recognise, deep down between the naked papillæ, in cells, only slightly larger than normal and globularly deformed, a ring-formed broken down edge and a centre, more deeply, often almost normally, stained ; the former is the protoplasm which has become cloudy, homogenised, and fibrinously degenerated with retraction of its prickles, the latter, the swollen and also homogenised nucleus. Further out we meet also globular but distinctly larger epithelial cells, which, if well stained, are seen to represent globular cavities, which contain in fibrinously degenerated, thin, expanded shells, a large number of epithelial nuclei. It is beyond doubt that these have increased by amitotic division, for one never meets mitosis in degenerated cells, and, on the other hand, the lines of separation are often evident on facetted neighbouring nuclei. These daughter nuclei frequently take the stain of healthy nuclei in a diminished degree, although the mantle of this epithelial giant cell is, and has long been completely degenerated. Along with this nuclear fragmentation, which may lead to the presence of twenty, thirty, or more nuclei in a cell, the epithelial cells, which are transformed into hollow spheres, swell up enormously, and it is chiefly these which stamp the vesicle with its remarkable form. The commonest form is that of a round ball or balloon drawn out to one side, and therefore

I propose to name the whole degeneration the ballooning, in contrast to the "reticulating." But they also present the form of many-handled baskets, of spiral tubes, and, taken together with their nuclear contents, they sometimes remind one strongly of the nests of the Weaver bird.

As in the reticulating colliquation a certain contrast exists between liquefied and compressed epithelial areas, and from the latter proceed the coarse rafters of the vesicle, so also in the ballooning colliquation, in addition to the round balloons, there are seen cord-like, compressed epithelial cells, which hang down from various parts of the covering into the interior of the vesicle and induce a form of septation. But these epithelial cells have undergone the same degeneration as the balloons, they are homogenised in exactly the same way and fibrinously degenerated, only the traction of the covering has drawn them out into long bands. At many places these flat bands pass directly into hollow nucleated tubes and round balloons. The slight lateral connection of the cells which distinguishes this degeneration from the reticulating, does not permit, on these more compressed epithelial areas, of the formation of firm trabeculæ, and thus there is no true partition of the vesicle. And therefore the neighbouring vesicles in a group of Zoster readily run together.

Now while, at the acme of the vesicular stage, the base of the vesicle, consisting mainly of naked papillæ, presents, loosely gathered together, the smaller ballooned epithelial cells, while groups of band formed, elongated epithelial cells hang down from the horny covering, while finally the central part of the vesicle contains degenerated epithelial giant cells, irregularly scattered and presenting all sorts of wonderful forms,—the remaining and chief part of the vesicle is filled with coagulated granular and thready fibrin. The liquid part of the Zoster vesicle is mainly inter-epithelial, in contrast to many other vesicles, especially small-pox. The rapid appearance of the Zoster vesicle is to be explained by the acutely developed specific degeneration of all un-cornified epithelium, which not only separates their connections, but converts the cells into a peculiar plastic, ductile mass. The power of this poisonous action in Zoster is particularly evident on comparison with other processes, where a similar one is present in less degree, as in variola. In that the ballooning degeneration affects only the youngest epithelial cells, in which marginal and internal protoplasm are not yet completely separated; all older epithelial cells undergo only reticulating degeneration, with partial retention of their cell mantle. But in Zoster the ballooning transformation attacks also the older epithelial cells, lying immediately under the horny layer, whose cell mantles present active resistance to the degeneration.

When the vesicles have attained this stage there commences a

marked emigration of leucocytes from the vessels. But this usually reaches no very great degree; though the papillary body is densely infiltrated by them. They make their way between the ballooning epithelia and reach, not only into the larger cavities filled with fibrin, but also into most of the large balloons, which generally show some rupture, so that one may recognise in them the vesicular pale epithelial nucleus, along with the deeply stained fragmented leucocytic nuclei. But the vesicle is never completely filled with leucocytes; before that stage is reached it dries up with all its fibrinous and cellular contents into a firm crust.

The importance and novelty of this make it advisable to present in tabular form the histological distinctions of these two distinct forms of epithelial degeneration.

Reticulating.	Ballooning.
Colliquation of the epithelial cells.	
1. The cells are from the commencement much swollen.	1. The cells are at first only rounded, without being distinctly increased in size.
2. The protoplasm becomes clear and stains less, but, for a time, in the ordinary way with basic stains.	2. The protoplasm becomes very cloudy, homogeneous, takes no basic, but on the contrary, acid stains eagerly.
3. Protoplasm shows at first no fibrin reaction.	3. Protoplasm shows from the first fibrin reaction.
4. The outer layer of the protoplasm, with the adherent prickles, is not so much affected with the colliquation as the inner cell substance.	4. The outer layer of the protoplasm, as well as the prickles, undergoes the same degeneration as the inner cell substance and is indistinguishable from it.
5. The nucleus does not undergo colliquation, and for a considerable time stains normally.	5. The nucleus also swells, but retains its normal staining capacity longer than the protoplasm.
6. At a later stage fragments of the nucleus break off; but true segmentation does not take place.	6. At a later stage the nucleus may, under certain circumstances, multiply amitotically.
7. In the œdematous protoplasm there appear vacuoles which run together and reduce the protoplasm to a meshwork.	7. No vacuoles appear in the protoplasm, only the nuclear cavity dilates and finally reduces the protoplasm to a thin shell.
8. The epithelial cells long preserve their connections, which never give way on all sides at once, but only in parts after great thinning of the marginal layer.	8. The epithelial cells at the commencement of the degeneration are converted into a collection of loose balloons and lose their connecting bridges.
9. The vesicle formed by reticulating degeneration of epithelia is essentially intra-epithelial.	9. The vesicle formed by ballooning degeneration is essentially inter-epithelial.
10. The vesicle is, in relation to the reticulating degeneration, at first multi-locular.	10. The vesicle, in relation to the ballooning degeneration, is at once unilocular.
11. The reticulating degeneration advances gradually.	11. The ballooning degeneration advances rapidly.
12. It attacks preferentially older epithelium.	12. It attacks preferentially younger epithelium.

(See Frontis., Figs. 10-13.)

Here I allow myself the historical note that my "reticulating colliquation" has usually been regarded as the only mode of vesicle formation, and therefore as corresponding, *e.g.*, mainly with Leloir's "altération cavitaire." On the other hand, Weigert's "anuclear fragments" in small-pox are probably more allied to ballooning degeneration; but the latter is only occasional in small-pox and is not formed in the perfection which so simplifies its estimation in Zoster.

Finally, Pfeiffer, in his discovery of "amœbæ" in many vesicular processes of the skin, was probably examining ballooned epithelia.

So far as concerns the pathological changes around and beneath this severe disturbance of the epidermis, they are relatively unmarked. Only in purulent and hæmorrhagic shingles, does the whole cutis share in the inflammation. In ordinary cases only the papillary body, directly under the vesicle, shows a dilatation of the blood vessels and lymph spaces, along with swelling of the connective tissue cells and a migration of leucocytes, at first only slight. This inflammatory area extends only the breadth of a few papillæ beyond the vesicle. Above this small inflammatory halo the epidermis is hardly altered, at most somewhat œdematous, contains neither mitoses nor an important amount of wandering cells. The blister with completely degenerated epithelium thus rises sharply from almost normal epidermis. This circumstance favours the view that, in Zoster, the presumptive parasites are in the epidermis itself, and chiefly exercise their activity locally.

After long existence, the blister extends itself somewhat beyond its original site laterally; the directly adjacent epithelial cells become very œdematous, and are sometimes affected with reticulating degeneration. These lateral pockets of the vesicle become filled with an ever-increasing number of leucocytes. The naked papillæ of the base are, partly from flattening, partly from their distension with wandering cells, no longer to be so readily distinguished from the ballooned epithelia now intermingled with leucocytes. Passing outward we see that the dilatation of the vessels and their sheathing with white blood corpuscles has considerably increased. But the latter are chiefly limited to the immediate neighbourhood of the vessels. The cutis in the further course of Zoster is only slightly permeated by leucocytes, but a slight œdema with dilatation of the lymph spaces and slight swelling of the collagenous substance, is evident all through it. The elastic fibres, with the exception of the fine, superficial processes in the papillary body underneath the vesicle, are everywhere well preserved. The coil glands do not share in the process, and the hair follicles only in so far as the prickle layer of the hair penetrating the vesicle is, for a certain distance downwards, also affected by the ballooning degeneration. The hair with its root sheath then lies loose in the middle of a collection of rounded, swollen, fibrinously degenerated and separated epithelial cells.

My preparations allow of no conclusions as to changes in the nerves. To this point future investigation, with appropriate methods, must be particularly directed.

Even during the acme, the process of restitution of the vesicle sets in, in that from all sides young epithelial cells containing true mitoses cover the base of the vesicle and thus encapsule the now pustular vesicle. The ballooned epithelia have no power of restitution. In the prickle layer of the surroundings we now first find numerous mitoses; and a few are seen in the endothelium of the capillary vessels. The leucocytosis of the base of the vesicle disappears, and the process, so violently commenced, returns to the normal. Only a thick crust, containing the whole pustule, gives evidence of the severe epithelial destruction. If the disease runs its rapid normal course no scars are left; unlike small-pox. Only where suppuration is prolonged, or where from the commencement there is necrosis of a whole vascular area, with consequent suppuration, do scars indicate the seat of shingles.

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C. INFECTIOUS INFLAMMATIONS.

The infectious inflammations of the skin form a comprehensive group, not only the richest in types of all groups, but also the one

which, by the discovery of new infectious agents and the recognition of the infectious nature of diseases, previously considered not infectious, is from day to day steadily increasing in extent. It falls naturally into two divisions—that of the *acute exanthems*, in which the exanthem is only one symptom of an acute general disease, and that of the *local cutaneous infections.*

The latter, with the exception of a few acute dermatoses (*e.g.*, Erysipelas, Pemphigus acutus benignus) are mainly chronic diseases, and are not so uniform and easily limited as the acute exanthemata. Only the first main group, that of the infectious diseases of the epidermis, the so-called "tetters," appears throughout as local diseases of the skin; the organisms causing them apparently can only vegetate in the epidermis and not in the tissues. But here and there we have an exception, as in the epidemic eczema recently described by Savill, in which a general disease followed on a local primary cutaneous one. And the group of Lichen planus, perhaps presents another such exception.

But this factor of the possibility or impossibility of generalisation does not hold in the second main group, that of the infectious diseases of the cutis. Erysipelas, Anthrax, or even a simple whitlow may cause the severest general infection, or remain purely local cutaneous affections, while Elephantiasas filiariosa and Glanders are not to be regarded as simple dermatites, however limited they may appear. And in a still higher degree this is true of the so-called infectious granulomata; Syphilis, Tuberculosis, Leprosy, and Granuloma fungoides. In their case, one is almost inclined to separate them completely from the local infections, and to place them as chronic exanthemata, in distinction to the acute exanthemata, in the group of general diseases with symptomatic affections of the skin. But apart from the fact that some of the most important infective tumours, such as the initial sclerosis and lupus, present themselves as inoculated local diseases and not as the results of a general disease, they are very different histologically from the acute exanthemata, and they closely correspond to those certainly local infectious processes of the cutis, tending to progressive growth of the tissue elements, such as Rhinoscleroma, the so-called Pemphigus vegetans, and Framboesia. But since those infectious granulomata stand much further from the actual tumours of the skin, both the malignant (carcinoma, sarcoma) and the benignant, than from many infectious inflammations without tumour formation, we will place them among the infectious inflammations of the skin, as a last group tending to tumour formation.

Before considering the individual members of this great group, it must be stated that in any arrangement, only the clinical and histo-

logical facts can be utilised, for of the etiology, the actual infective cause, our knowledge is too deficient and in particular too unequal. Only of a few of these infections can it be said that our etiological knowledge is as complete as our anatomical and clinical, as for example, in Tuberculosis, Impetigo staphylogenes, Trichophytosis, Scabies, Erysipelas. In other, certainly not less infectious processes, *e.g.* Syphilis, Aleppo boil, Impetigo contagiosa, we have scarcely or not at all the first rudiments of etiological knowledge. In others we have noteworthy commencements of a better knowledge; but they still require confirmation from other investigators, as in Eczema, Psoriasis, Erysipeloid, Acne varioliformis, Ecthyma, Ulcus molle. Other processes are so nearly comparable to better known infectious skin diseases that, without etiological recognition, their provisional installation is justified, *e.g.* Tinea imbricata, Impetigo herpetiformis, Parakeratosis scutularis, Lichen planus, Pemphigus acutus benignus, Folliculitis Lukasiewicz, Spiradenitis, the so-called Pemphigus vegetans, etc. Finally there are some, of which the etiology appears to be already determined by certain investigators, but is generally contradicted, as in the Psorospermosis of Darier and in vaccinia.

It will therefore not appear strange, if, supported by purely anatomical and clinical grounds, we rank here a series of skin diseases whose infectivity is as yet partly not suspected, partly directly denied, and as yet not certainly determined, in the sure hope that the future will establish their position, as it has done for so many other affections in the last ten years. As such, for example, I regard Pityriasis rubra Hebra, Pityriasis rubra pilaris, Pemphigus chronicus, Acne and Ichthyosis. The justification of this will appear, partly from their histological peculiarities, as these are described, and partly from the clinical relations, which here are only suggested.

I place the local infectious inflammations of the skin before the acute exanthemata, for this group permits of systematic sub-division and therefore aids in the comprehension of the few but very different acute exanthemata.

1. Local Infectious Inflammations.

($\alpha\alpha$). Local infectious Inflammations of the Epidermis.

According to our chemotactic doctrine of inflammation, a chemically induced attraction of exudation, with its different results of nutritive, proliferative or exudative appearances, may affect the epidermis just as well as the cutis. It is not owing to the vascularity of the tissue that it inflames, for the fluid and movable constituents may be attracted from a distance and may be again fixed, far from their point

of origin. Indeed that tissue is most "inflamed" which swells up most, because it is the centre of attraction of the exudation. Certainly we must describe as inflamed the whole region through which the exudation passes and in which it has left traces of its presence, in particular all tissue, which shows by its change that it has been reached by the exudation following the chemotactic irritant.

Thus in epidermic inflammation we must have, inside the epidermis, some inflammation-causing agent; the inflammations here require that a local infectious agent must be present. But the inflammatory sphere may be of very varied extent, it may, in rare cases, be limited to the epidermis, or reach more or less into the cutis. Very often, and this is a simple consequence of the chemotactic theory of inflammation, it is limited to the blood vessels next the epidermis and its appendages, for these provide the exudation to the chemotactic irritant. This is the reason why so many epidermic inflammations affect the papillary body and it alone, a fact which, along with others, has led Kromayer to combine papillary body and epidermis under the name "Parenchyma skin," and to speak of a common inflammation of it as a unity in the pathologico-anatomical sense. I would gladly adopt this view were the individual inflammatory diseases strictly limited to this region. But, as will be seen in the course of this section, there is a whole series of typical, exudative epidermic inflammations, which take place almost exclusively in the epidermis, and others, and very important ones, such as eczema, which if they last long may also affect the deeper layers of the cutis. So that this definition would lead to a confusion between the epidermic inflammations in the narrower sense and the inflammations of the appendages, the follicles and coils. For then we would be equally right in regarding the vascular connective tissue immediately around the follicles and coils, together with these, as a unit. But here comes in an exception to the rule; the inflammations of the appendages are very rarely limited to their immediate surroundings. In almost every case (Acne, Sycosis, Trychophytosis, Favus) the inflamed region reaches far in all directions into the cutis—in this only proving the chemotactic theory. For the scanty capillary net is not in most cases sufficient; the exudation is attracted to the follicles from a much wider distance.

As in many other cases, the chemotactic theory has here proved a useful guide in recognising important and unimportant factors in inflammation. If one follows it, he will not object to the diseases here grouped together as inflammations of the epidermis or to their further division into superficial and deep, according as the seat of the inflammatory agent is found in the surface epithelium itself or only in the appendages. The extension of the inflammatory irritant may vary

very much; there are no lines laid down for it, it depends in each case entirely on the strength of the irritant.

(*aa*). Superficial Inflammations of the Epidermis, Cutaneous Catarrh.

The superficial inflammations of the epidermis comprise what is popularly known as "Tetter." The name *cutaneous catarrh*, introduced by Schmidt and adopted by Auspitz and myself, indicates the same important group of diseases. The laity speak of "*wet*" and "*dry*" tetter, physicians of "moist" and "dry" catarrhs of mucous membranes, and thus this group, according to the external symptoms of greater or less exudation, may be divided into the *dry* and *moist cutaneous catarrhs*. In both classes there are dermatoses which always preserve their moist or dry character, but there are also others which, in different individuals or regions, at different times or in different stages, appear sometimes moist, sometimes dry. Thus it is seen that the two sub-divisions are by no means mutually exclusive, but on the contrary are very nearly allied. Eczema, which I have placed here, as a whole, with the moist cutaneous catarrhs, comprises a series of forms which typically represent "*dry cutaneous catarrhs*," and it is therefore the best proof of the relationship of the two groups. On the one hand, eczema now and again shows impetigo-like, primary eruptions, and again, at the acme of a previously dry cutaneous catarrh, vesicles and weeping. To these types of eczema may be added a whole series of vesicular diseases of the epidermis, especially the purulent and fibrinous impetigos, and they constitute, along with pemphigus and ecthyma, the group of moist cutaneous catarrhs.

But on the other hand, eczema begins in most cases with a scaly spot or a dry scaly papule—though this has long been over-looked—and another acme stage of the chronic eczematous catarrhs is a typically dry, scaly, keratoid condition of the surface. Were the division of the disease to be undertaken afresh, possibly many of these dermatoses might be reckoned to the dry cutaneous catarrhs. But we stand historically in the shoes of Willan-Batemann, and the name "eczema" has since their time been too closely bound up with the idea of a vesicle to be again separated from it. In other dermatoses, it is just the same; we are familiar with a dry stage of the typically bullous disease of pemphigus; Pemphigus foliaceus; Trichophytosis may produce on the surface scales instead of vesicles; Erythema multiforme Hebra has its moist representative in Herpes iris. In all these cases it has long been the habit to stamp each disease with one definite mark as especially typical, pemphigus with the bullous character, and so on.

It does not appear to me particularly important whether one puts

one or other of these diseases in the group of moist or dry cutaneous catarrhs, it is more important that by adopting this grouping, the natural relationship between apparently very different affections is justified. Nor is it of great importance whether the moist catarrhs are called eczematous, from the most important disease of the group. It is more important that one should indicate the dry catarrhs as *Parakeratoses*, for this name has a histological significance and a scientific meaning. The definition was originally established and very narrowly restricted by Auspitz; especially for Auspitz's Psoriasis-Lichen-group. In recognising the nature of this anomaly of cornification in an abnormal degree of moisture of the cornifying transitional layers, I must widen the definition of parakeratosis. Clinical facts had already led me considerably to widen it; now I recognise that, between the parakeratosis of psoriasis and that of the dry forms of eczema, there is no important difference. Thus the parakeratoses represent to me a dry contrast to the moist cutaneous catarrhs, though they are only "macroscopically dry." The moisture, which is externally visible in the moist cutaneous catarrhs, is only restricted because in general it is less; but it is present typically in the anomaly of the margin of cornification. In the histological investigation of psoriasis-like dermatoses accompanied by scaling, it is clear that the histological criterion of parakeratotic transitional layer (absence of kerato-hyalin, preservation of the nuclei, abnormal moisture) is not sufficient to characterise all the dermatoses belonging to this group. There is a series of very superficial chronic inflammations of the skin, which show an abnormal condition of moisture of the epidermis, too small, however, to lead to a parakeratotic transitional layer. It only suffices to give to the horny layer a less brittle character, a greater coherence, and thus leads to the piling up of scales on apparently normal or almost normal transitional layer. Here also we have an abnormal cornification, but it is not the real genuine parakeratosis. These dermatoses (Pityriasis rubra Pilaris, Lichen neuroticus, Lichen planus, Ichthyosis, etc.) are certainly dry cutaneous catarrhs, but not parakeratoses in the narrower sense of the word. That there is latent in them an abnormal epidermic moisture is evident clinically, for most of them show, sometimes regionally, sometimes temporarily, moist stages (Eczema ichthyoticum, vesicles in Lichen planus, weeping in Darier's disease). Should we therefore remove these "hyperkeratoses" from our group of dry cutaneous catarrhs of which they have all the other symptoms, simply because they do not or only locally show "parakeratosis optima forma"? I think not. There are two possibilities. Either we widen the definition of parakeratosis to include all anomalies of cornification. Then we would once more have the group of parakeratoses. Or—and this

appears to me better—we retain the term of parakeratosis for that main anomaly of the margin of cornification in the narrower sense and give it up as a character of the group. Then we preserve the easily understood and descriptive name of *dry cutaneous catarrh.*

The justification of admitting lichen planus, in virtue of lichen neuroticus, into the circle of this group of dry cutaneous catarrhs will be evident from the histological description. But I by no means deny that lichen planus, above all the dermatoses of this group, has most analogies with certain diseases of the cutis—a problem for future study.

To the superficial epidermic inflammations there belong strictly two other diseases: the superficial favus (Favus herpeticus) and the superficial trichophytosis (so-called Herpes tonsurans squamosus et vesiculosus). I have considered these with the deep inflammations of the epidermis, along with the deep follicular forms of the two fungus affections, so as not to destroy the connection.

(α). *Moist Cutaneous Catarrhs.*

The section of the moist cutaneous catarrhs is, rather remarkably, only at the commencement of its investigation, though it is quite as rich in interesting and instructive facts as the group of dry cutaneous catarrhs, which have received plenty clinical and histological attention. This is well shown in the striking deficiency of works on the histo-pathology of eczema compared to the great number of those on psoriasis. Further, the definition of eczema of Hebra's school, which in many directions is too wide and embraces all those forms of isolated vesicles and crusts, which I treat here as different forms of impetigo, has made the matter much more difficult. For these affections are mostly diagnosed as "eczema," and this makes neither them nor the definition of eczema any clearer. So that I have found it necessary to introduce no fewer than eight dermatoses into this chapter, and in this I only make a selection of affections which I have recognised, for I only introduce as examples, those which appear to me histologically to have a special interest. But I hope that the reader of this chapter will agree with me, that in the whole cutaneous pathology there are few affections which are so instructive as these impetigines. For the ideal of histo-pathology is achieved; histological investigation at once explains both the clinical and the pathological course. Here we see in almost every case the infectious agent in intimate connection with the cutaneous tissue, whose reaction leads to the clinical appearances; and the soil on which this goes on is small enough to be surveyed in one single section.

Here we first see that every different parasitic organism corresponds

to a different reaction of the tissue, and as we shall, remembering the histological facts, better observe clinically, we become convinced of the absolute difference of such apparently similar clinical diseases. I recommend every investigator especially to the study of impetigo ; for here we see, in brief, what clinically is really pathologically important. And I also recommend its study to every pathologist, for nowhere will he see so clearly and easily the genesis of the inflammatory process.

After having stated in different places that there are no two affections, and especially that there are no two inflammations, which run exactly the same course, I will not be misunderstood, if I subdivide the affections according to the character of the exudation. This I do only to summarize, because the fewer groups we have, the more justice we do to the individual affections which are placed in them. And first there are some affections which may be grouped according to their **purely serous** or **purely purulent** character. Among them there are some whose exudation is mainly serous, but contains, either at the commencement or later, a mixture of fibrin and leucocytes. In order not to have too many divisions I have formed of these dermatoses a complex group, that of the **leuco-serous** and **sero-fibrinous** cutaneous catarrhs. Finally there remain those affections in which the exudation from the commencement is very rich in fibrin and leucocytes ; **the leuco-fibrinous.** I do not lay much stress on the retention of this arrangement, because the immediate future will teach us a large series of other diseases of this class, which will perhaps join these groups or lead to the formation of new ones.

(*a*). Serous Inflammations.

Scabies.

The itch mite (Acarus scabiei) produces on the skin a moist cutaneous catarrh which I place before the others of this group, because, on account of the size of the parasite, the conditions are very clear and easily studied. The scabious catarrh occurs in two types ; one acute, with the vesicle as the primary appearance, ordinary scabies, the other a rare form with a chronic course, so-called *scabies norvegica.* Of course in spite of the acute course of the individual spots, the first form may also run a chronic course.

A. *Scabies vulgaris.*

The mites burrow first obliquely into the horny layer until they reach the firmer basal horny layer, and then, leaving behind them ova and fæces, make their way above the basal, inside the central horny layer, parallel to the surface. They form in this way burrows several centimetres long, straight or somewhat crooked, whose covering is somewhat arched over the surface of the skin, and in whose distal, blind,

often somewhat swollen end the mite itself is found. The mites thus dig in the epidermis what miners call galleries, not shafts, and these are found, not as is stated in most text-books, but simply inside the horny layer (Török). The penetration of the mite itself into the prickle layer is improbable, even on clinical grounds. For if the mites were seated, as is usually believed, in the prickle layer, not only would there be constant considerable pain, but serum would always be pressed from the burrows; and severe inflammation and necrosis of the prickle layer must in all cases be the invariable result. While the true clinical symptoms; more or less marked vesicular formation under the burrow, greater or less periodic itching, fit in very well with the histological fact that the mite lives in and from cornified epithelium.

The immediate surroundings of the mite, the wall of the burrow, become, from the entrance of air and the pressure of the mite, dry and hard, so that the burrow does not collapse, but preserves in its breadth and height the size of the body of the mite. Its base is covered with large brownish black masses of fæces and the usually transversely placed eggs, which show a series of progressive stages of development from the mite to the outer end of the burrow. But many burrows are mainly or completely free from ova, while scybala are found in every one. This makes it possible for the histologist to decide definitely in every case whether scabies is present or not.

Were there no further changes produced by the immigration of the acarus in the skin than the galleries in the horny layer and the condensation of the epithelium, the scabies mite would come in the class of saprophytes. But there are invariably found, in the living parts of the skin, appearances of reaction of an eczematous nature, which justify the inclusion of scabies among the moist cutaneous catarrhs.

In the mildest degrees we have only a dilatation of the inter-epithelial lymph spaces and a slight swelling of the prickle cells underneath the burrow, and in addition a few leucocytes. But usually about the granular and the upper prickle layer some lymphatics dilate to inter-epithelial vesicles, which rapidly enlarge, compressing and displacing the rest of the prickle layer. Usually these vesicles have a sharp margin, and are surrounded by stretched, but otherwise healthy cells. They contain sometimes perfectly clear lymph, which, in alcohol sections, is finely granular, and in osmium sections shows reticular coagulation, and there is a varying but never considerable amount of leucocytes. Pustules beneath the burrow always indicate the addition of pyogenic organisms. If the vesicles persist, some of the epithelia of the wall swell up and fall into the vesicle, especially at its apex directly underneath the horny layer. But these changes are so slight that one can hardly speak of secondary degeneration of

the prickle cells. Above the vesicle the granular layer has usually disappeared and the basal horny layer is swollen. There we sometimes have the formation of small vesicles of the horny layer, which are seated between the burrow and the larger vesicles of the prickle

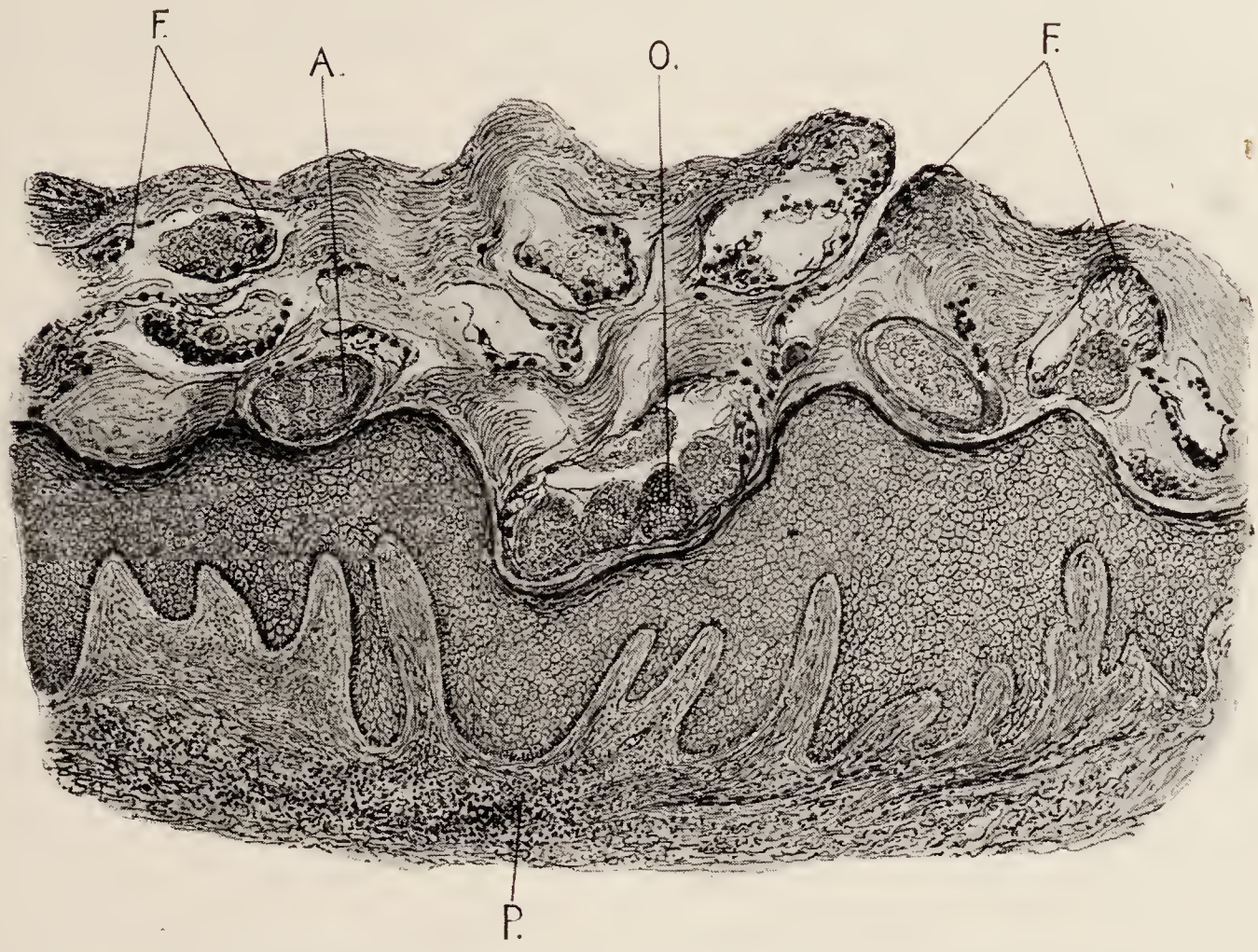

FIG. 3.—Scabies. Showing the position of the acari in the horny layer.
A. Acarus. *O.* Ova. *F.* Fæces. *P.* Plasmonatic infiltration.

layer. Under such circumstances the vesicle may burst into the duct, and this will of course lead to a saturation of the latter with tissue juice. The vesicles of the prickle layer may be considerably distended, the horny layer elevated with the burrow and the basal prickle layer pressed downwards so that the papillary body is depressed. But the vesicle never oversteps the margin of the cutis, as pustules may do, and without secondary infection its character never becomes purulent, although with age more and more leucocytes collect in it and the epithelium around. If the burrow is separated, in a very thick horny layer, from the basal layer by a considerable number of horny cells, we find, instead of the vesicle formation in the prickle layer, only a swelling of the transitional and basal horny cells into large homogeneous fragments. If, on the other hand, the burrow reaches to the transitional layer, it tends to be surrounded by a number of layers of cells, which are swollen, enlarged, and homogenised, and in which the individual layers of the granular cells and basal horny cells are no

longer to be recognised. This zone of transitional epithelium, swollen and compressed by pressure from above, takes the place of the basal horny layer in protecting the prickle layer from the burrow.

Where the inflammatory process has reached vesicle formation, there are marked changes in the cutis. First, there is a more or less pronounced œdema of the papillary body, whose blood vessels are dilated and whose fixed connective tissue cells are enlarged and multiplied.

Mitosis is evident on them and on the endothelia of the blood vessels. The prickle layer between the vesicles shows numbers of leucocytes and a very few mitoses.

Ordinary scabies is, therefore, to be recognised as the type of a vesicular catarrh of the skin. The parasite remains far from the changes of the prickle layer, but its unknown products penetrate into it. It is not necessary to assume that these reach the vessels and injure them, and thus the exudation is a reaction of the injured vessels towards the neighbourhood of the parasite. The substance in question only needs to act chemotactically on blood serum and less on the leucocytes, and the attraction into the neighbourhood is explained, as is the ordinary localisation of the vesicle close under the horny layer, for there the exudation first meets a hindrance. In favour of a pure, uncomplicated chemotaxis is the slight degree of dilatation of the vessels which accompanies the inflammatory process. Similar conditions: seat of the parasite in the horny or transitional layers, chemotactic action on the papillary body, its lymph and wandering cells, we have to constitute in all epidermic catarrhs.

It is a question of equal theoretical and practical interest—what is the nature of the large serous or purulent vesicles which appear in long-lasting scabies, mainly where the patient is dirty. The latter favouring condition, as well as their difference, and the fact that these vesicles may be absent in certain cases, indicate their development by secondary infection with micro-organisms. Here microscopical investigation must decide. I have, therefore, removed two large vesicles from the hand, which were both in the immediate neighbourhood of burrows; one was transparent, the other, larger, yellowish, and opaque, appeared to represent a further stage of the former. The latter consisted of a pure sub-corneal pustule, over whose centre was a tear in the horny layer. In this were numerous staphylococci, which extended in all directions on the under side of the horny layer, and between it and the pus. The latter was completely free from cocci, and in particular there were no leucocytes which had taken up cocci. The vesicles were completely packed with leucocytes, without any admixture of serous or fibrinous exudation. The compressed prickle

layer was completely normal, except for the compression; there were no groups of cells loosened and cast into the vesicle. Consequently it was a typical impetigo staphylogenes. To my astonishment the second vesicle close by was quite different. Here also, there was a subcorneal compression vesicle, but it was not filled only with leucocytes but mainly with serum and fibrinous coagula, varying with numerous groups of leucocytes. Here also, exactly over the centre of the vesicle, there was a tear in the horny layer, but it was not filled with staphylococci but with morococci. These were not extended under the horny layer, but were mixed with the contents of the vesicle, and reached to its base, and they were everywhere found in the leucocytes in the form of diplococci, often in quantities. The surrounding prickle layer was softened, permeated by wide spaces filled with leucocytes and serum, and even the horny layer of the surface showed a lesser degree of loosening. In short, this was a typical acute eczema vesicle.

Both vesicles corresponded in not communicating directly with the burrow which lay laterally above them, though separated from them. Consequently the only explanation is that both vesicles were inoculated by the patient scratching the burrow, the one with staphylococci, the other with morococci.

According to these observations on postscabious vesicles, it is beyond question that these may differ in every case, and that in general they are always due to some secondary infection, which the patient has conveyed by scratching. That during long-lasting scabies we may have both true chronic eczema and furunculosis, both of which may last after the scabies, is a well-known clinical experience. Whether an infection of the true scabious vesicles with micro-organisms by the mite itself and thus their transformation into large vesicles and pustules ever occurs, further investigation must show.

B. *Scabies norvegica.*

This is a modification of the scabies process, in which, instead of the acute vesicular catarrh, we have a chronic change of the epidermis, proliferation of the prickle layer and the formation of horny shields. It indicates long undisturbed activity of the mites, and there must, therefore, be less sensibility of the patient or less irritation from the parasite, perhaps both.

In these cases, the preparations of which I owe to Dr Riehl, the acari are also found only in the horny layer, but this is very much thickened and penetrated, not by simple galleries but by a complicated system of burrows. Most of the burrows run obliquely or almost horizontally and in rows over each other, and they are everywhere connected by lateral passages. The youngest burrows are found

directly over the basal horny layer, the oldest ones in the terminal layer; they form altogether a communicating system of spaces, in which full grown acari, a great number of eggs and, corresponding to the age of the mine, a mass of fæces are found. While in the ordinary form of scabies the young mites, escaping from the eggs, make their way to the surface of the skin and dig out new burrows for themselves, in this case they penetrate laterally into the horny layer, where they find normal horny substance, without going to the surface of the skin. The epithelia which form this thick crust are provided in abundance by the prickle layer, which is distinctly hypertrophic and shows numerous mitoses. The papillary body also shows symptoms of chronic irritation in the abundance of large connective tissue cells, especially vascular perithelia. While the ordinary form of scabies is the type of a moist cutaneous catarrh, scabies norvegica is the type of the dry epidermic catarrh. We will also have in eczema to distinguish moist and dry forms, a difference which, as scabies teaches, by no means contradicts the etiological unity.

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Impetigo serosa, simple serous vesicles.

A little girl of eighteen months suffered for some weeks from a vesicular affection. The vesicles affected mainly the upper half of the face, hairy scalp, cheek, chin, and inguinal region, and had a certain resemblance to vaccine vesicles.

This vesicular affection is the simplest conceivable type of a subcorneal phlyctenula. The vesicle is monolocular and the horny layer forms the cover, the compressed prickle layer the base and the sides. The contents consist of serum (coagulated by alcohol) without any fibrin, any white blood corpuscles or any detached epithelia. While thus the form of the vesicle recalls that of staphylogenic impetigo, the contents consist in one of pure serum, in the others almost entirely of leucocytes. As in impetigo staphylogenes, the causal organisms are found at the vault of the vesicle, directly underneath the horny layer, but they are not ordinary staphylococci, but other iodine resisting cocci, which, held together by mucus, form smooth rounded balls. Such a ball is found exactly under the centre of the covering, and in the neighbourhood of the upper part of a sweat pore, whose upper two turns, filled with cocci, are torn from the rest of the duct and elevated with the cover; we have before us the very exceptional occurrence of an infection through the sweat pore. This is of course

only possible when the micro-organisms do not suffer from the very acid reaction of the sweat.

The complete absence of leucocytes, and the want of scattering of the cocci or their presence in leucocytes, distinguishes this vesicle from the acute eczema vesicle, which it somewhat resembles in the amount of exuded serum.

The cutis beneath the vesicle is completely normal, the blood vessels are hardly noticeably dilated. Except for flattening, the papillary body is normal, as is the epithelium around. It is a purely serotactic process taking place in the epidermis.

Impetigo protuberans.

Frau L., 65 years old, skin previously healthy. Six weeks previously there appeared, on the back of the right hand, red papules and vesicles, which slowly spread over the left, then the right arm, the legs, buttocks, neck, throat, and finally over the cheeks, without anywhere spontaneously healing. Except for a very few vesicles the trunk is free. All the spots itch severely. The vesicles are one mm. in diameter, and after some days are converted into small elevated brown crusts which remain long adherent. Most of them undergo further development, being surrounded by a red halo three to four mm. broad, and one to two mm. high. The vesicles, seated on the apex of the dark bluish-red papules, dry up without enlarging into thin crusts ; but if they persist, there appear beneath the peripheral border of the crust secondary vesicular protuberances $\frac{1}{2}$-1 mm. in diameter, which project somewhat over the central crust, are thick skinned, yellowish, and transparent. There usually appear simultaneously, two, three, or four such marginal vesicles, which, without running together, surround the crust, and these are surrounded by the red border of the papule. There are very often four vesicular protuberances arranged at the corners of the central crust, thus giving the papule a quadrilateral appearance. The papule is gradually covered with a somewhat larger crust of very irregular form. The contents of the vesicle are clear and yellow, there is little fibrin and no pus. All the papules and vesicles are sharply margined, have no tendency to run together, and are of a remarkable resistance and duration. They are closely distributed all over the affected parts without any connection with the follicles.

The histology of this form of impetigo is as peculiar as its clinical appearance. The difference between the primary central vesicles and the marginal vesicular protuberances is very clear. The former is a serous sub-corneal vesicle containing few leucocytes and threads of fibrin. This distends the prickle layer downwards and stretches to a maximum the prickle cells, so that in long-standing vesicles, spaces appear at the base, through which the vesicular contents communicate with the œdematous papillary body. The covering of the vesicle, consisting of horny layer and containing a moderate amount of fibrin and leucocytes, is not projected, but stretched flat, very firm, and we see that the marginal vesicles arise over the level of the depressed,

deepened central crust. They contain a great quantity of cocci of a definite variety which usually form large rounded collections. The cocci are small, 0·6-0·7μ, spherical, without any definite capsule, but the collections show a regular arrangement. The innermost cocci in the larger collections and those in the outer parts of the crust are sometimes twice that size, and are to be regarded as diplo-cocci undergoing cleavage. The prickle cells, which form the surroundings of the vesicle, show no degenerative changes, but only widespread interspinal œdema, which, immediately around the vesicle, near the horny layer, leads now and then to the formation of small epithelial cavities, filled with serum and leucocytes. The papillary body underneath the primary vesicle also shows a definite œdema, shown not only by the dilatation of the lymph spaces but by the œdematous swelling and rounding of the connective tissue cells. Most of the round cells, which fill the flattened and depressed papillary body under the vesicle, are such rounded spindle cells and not leucocytes, which, with good stain can very easily be distinguished from them, and which in this process play only a subordinate rôle.

Quite another appearance have the vesicular protuberances which appear later under many of the crusts, after the vesicular base has been swollen by inflammatory œdema. These are no true vesicles, which term we restrict to exudative spaces in the epithelium, but enormously enlarged œdematous papillæ, some of them converted into true serous cavities. Here we find on the contrary the supra-papillary prickle layer pressed outwards and thinned, the inter-papillary ridges compressed into thin processes and excavated. The connective tissue of the rounded swollen papillæ is completely separated, and the fine, persistent collagenous fibres are difficult to distinguish from the rafters of coagulated serous exudation which run through this pseudo-vesicle. A special interest have the connective tissue cells of the œdematous papillary body. They are all spherical and contain two, three or more closely packed, oval, large, pale nuclei. The granular protoplasm is displaced and appears in the form of dark blue (methyl blue orcein) granules at their periphery. The spongioplasm is in general distended by the œdema of the cell into a net of large round meshes. Often it is quite light, almost unstained, and the cell gives the impression of a round basket consisting of rounded meshes, containing the facetted, compressed nucleus. In other cells some of the meshes are filled with pale, little stained granular protoplasm. Other cells again show a solution of the protoplasm at the periphery of the cell, fine threads hanging, as if torn, on all sides, so that the diminishing cells lose their previously sharp contours. At the under margin of the œdematous papillæ we can study the gradual transition of the large spindle cells

with well-developed spongio-plasm into these œdematous cells ; first the processes are retracted, the cells round off and swell up, every single mesh of the spongioplasm becoming spherical, more faintly stained and finally quite transparent.

The elastic substance is completely absent in the œdematous papillæ, the collagenous tissue is distended and in some places disappears, leaving true spaces filled with serum. Leucocytes are sparingly present in it, recognisable only by their homogeneous protoplasm and their clover-leaf nucleus. The few mast cells which are present undergo a very remarkable change ; they also become spherical and transparent, and are only to be recognised by their red colour (methyl blue stain) but this mainly stains not the specific granules ; it is diffusely spread in the œdematous cell body and partly washed out. Only a few well-stained granules remain. The œdema consequently leads to the solution of the mast cell granulation.

This papillary œdema extends, according to the age and size of the papule, in varying degrees towards the sides, and attacks one, two to six papillæ. The peripheral zone which corresponds to the vesicular protuberances is then distinctly broader than the central vesicle. But this also extends in breadth and depth with the increasing size of the papule, and in a very characteristic manner, an extension which corresponds with the clinically evident enlargement of the crust. Where the central vesicle enlarges laterally it does not do so by penetrating the spaces developed from the liquefaction of the papillæ, but forms a new inter-epithelial cavity above the liquefied papillæ, in the previously thinned and compressed prickle layer. These small lateral cavities enlarge and finally unite with the central primary vesicle, which therefore laterally enlarges only at the surface. As far as this takes place there is formed a new crust, containing fibrin and leucocytes, which unites with the old crust. Beyond that the crust does not extend, however great the œdema and however vesicular the peripheral border may appear ; over the simply papillary œdema with maximally thinned epidermis, no crust is formed. The persistent central position and the irregular advance of the crust is therefore readily comprehensible.

The central vesicle also enlarges downwards, but here the œdematous papillary body unites with the vesicles. Only with a good collagen stain can we still recognise the border, and only a good protoplasm stain shows us some groups of epithelia, which indicate the under border of the original vesicle. In these older vesicles there are found numbers of leucocytes, the epithelial remains in the vesicles are washed out and only faintly stained. The cocci are recognisable so far as the crust formation reaches.

The characteristic complete papule with its crust and marginal vesicles thus consists mainly of the papillary body, distended to a maximum by œdema and containing in the centre a compression vesicle. On it follow laterally in the epithelium supplementary vesicles, separated by rafters of cells, and so far as these reach, the spot is covered by a firm thin crust containing cocci. Underneath this, laterally, there is an excessive papillary œdema, by which the periphery is usually elevated at certain places (protuberances). This explains the thick covering and the absence of a tendency to confluence, by which these protuberances are distinguished from the marginal true vesicles of other impetigines. The slight implication of leucocytes and fibrinous coagulation is also evident histologically. It is then a very interesting form of serous epidermic inflammation, with special implication of the papillary body.

Pemphigus.

In defining Pemphigus I exclude the so-called "Pemphigus vegetans" (Erythema bullosum vegetans), the so-called "Pemphigus conjunctivæ," the so-called Pemphigus pruriginosus (Hydroa), the so-called Pemphigus circinatus, confertus, gyratus (all of them cases of Erythanthema bullosum), the so-called "Pemphigus syphiliticus" (bullous syphilide), the so-called "Pemphigus leprosus" (bullous neuro-lepride), the so-called "Pemphigus neuriticus and hystericus" (vesicular eruptions resulting from inflammation and wounds of the nerves and from hysteria), and finally Impetigo contagiosa, identified by some as Pemphigus acutus neonatorum; and I understand by *Pemphigus: only those bullous diseases in which watery, non-purulent vesicles appear in different parts of the body on unreddened or moderately reddened skin, in irregular order or in periodically occurring general outbreaks, but without the formation of characteristic groups or rings, are at most regionally distributed and symmetrical, and appear rapidly, with remarkably little subjective disturbance.*

Transient erythanthemata at the seat of the vesicles, angiogenic symmetry, angiogenic grouping, severe pain or itching, primary purulent contents in the vesicle, exclude the diagnosis of Pemphigus. The definition comprises not *one* vesicular disease but a small *group*, whose members are very similar in regard to the eruptions but differ much in regard to the duration and severity of the disease. Probably they are all of a parasitic nature, and depend, to judge by the clinical appearance, on the invasion of different organisms.

We have:

A. Pemphigus acutus benignus afebrilis.

B. Pemphigus acutus malignus febrilis.
C. Pemphigus chronicus, with its malignant development into "Pemphigus foliaceus."

A. *Pemphigus acutus benignus afebrilis*

is an eruption appearing, without fever, and in a short time affecting the greater part of the body. It consists of watery blisters of the size of a lentil to a pea, or larger, whose contents after some days become cloudy, but rapidly dry up, without becoming purulent. This form appears as an epidemic among new-born children, more rarely in adults, and is then usually conveyed by inoculation from children. From the impetigo vulgaris, which so often endemically attacks children of poor nutrition, this acute pemphigus is distinguished by the greater thickness of the cover of the blister, its considerable watery contents, and its longer existence; the thinner and paler crust containing little fibrin, the lesser hyperæmic base, and finally by the absence of the characteristic topography of this impetigo, a predilection for exposed parts of the body. The epidemic Pemphigus neonatorum has been up to now less easy to separate from the *epidemic* Impetigo contagiosa; on the famous Wittower epidemic of the latter in Scandinavia, there directly followed several of epidemic Pemphigus neonatorum. Only bacteriological examination can definitely separate the two diseases.

Equally difficult is the separation of the acute afebrile pemphigus from certain bullous pemphigoid eruptions in children, which run their course without fever, and which, in their recurrences, closely resemble the chronic pemphigus of adults. I have consequently described, under the name *pemphigoid eruption*, the anatomical characters of such an infectious eruption in a child, which was for years considered pemphigus.

The anatomy of this form of pemphigus is still to be discovered, and it will be necessary, in view of the affection of new-born children, to be particularly attentive to the actual differences of the affection of the skin at the different ages.

B. *Pemphigus acutus malignus febrilis*

appears with general symptoms (fever, vomiting, headache, stupor, delirium) scattered all over the body in the form of small or larger watery blisters, whose contents sometimes become cloudy, and, after bursting, leave moist surfaces, almost without epithelium. Frequently, reddened itching or burning spots precede the blisters. This condition, which points to an embolic development, as well as the affection of the whole body and the serious condition (I have seen a case end fatally in less than a week) stamps *febrile acute pemphigus* as a general (septic) disease, especially affecting the skin, *i.e.*, a variety of acute exanthema (Senator). A purely epidermic afebrile stage may precede the septic period of the disease.

It would be desirable to remove this form (Febris bullosa of the old writers) entirely out of the pemphigus group, then one would have at least only *afebrile pure skin diseases* comprised under the name pemphigus. This disease would then be ranked with *Pustulosis staphylogenes* and *Phyctænosis streptogenes*, as a special variety of *Phylctænosis.*

Of this affection we have very recently the anatomical examination of one case by Buckler, which was clinically observed by Bleibtreu.

The densely filled fresh blister proved, on section, to be single and had arisen through elevation of the horny layer, to which remains of the prickle layer were still adherent. The prickle layer in the neighbourhood was œdematous, and further, in relation to the blister, whose base it formed, was folded and permeated by leucocytes. The absence of cellular infiltration in the corium was remarkable, only around the papillary vessels were the nuclei increased. On the covering and in the prickle layer of the base of the blister there were found enormous numbers of cocci, arranged in clusters of three to fifteen or more; they were rarely single. Some were of the size of ordinary staphylococci, some larger, about the size of gonococci. In a second spot, from which the covering had been removed, there were found, in addition to Saprophytes which had come from outside, the same cocci in the base of the blister and some in the lymph spaces of the cutis.

Claessen, who cultivated the organisms of this case, regarded, as the actual infectious organism, a diplococcus which resembled "with slight variations" that from Demme's case. They showed, however, the considerable size of 1·8 to 3μ (certainly in the hanging drop), while Demme suspected as the actual cause, in his case, a small diplococcus of ·8 to 1·4μ. As Demme's case has been the most carefully examined bacteriologically, we may further say of it that the diplococci formed on agar, after thirty-six to forty-eight hours, a milk-white circular drop-like layer, which first extended concentrically, and then by the pressure of nobby prominences developed into a cream-coloured rosette. The diplococci were pathophoric for guinea pigs, but caused no bullous affection.

Of the other discoveries of Bacteria in Pemphigus acutus febrilis we need not further speak.

C. *Pemphigus chronicus.*

Watery bullæ which appear on all parts of the body, sometimes singly, sometimes in patches, with or without long intervals. The eruption may last for months and then definitely heal, or it may last with indefinite recurrences for years, even decades. Neither the duration nor the number of blisters determines the prognosis, but the eventual development of a deeper skin disease, the always malignant transition into the so-called *Pemphigus foliaceus*, in which the skin is affected throughout its whole thickness, and the porosity no longer permits the formation of blisters, but only of flat scales. Of less importance is the appearance of papillary excrescences on contact surfaces, if these have been long affected with blisters. These cases must not be confounded with *Erythema bullosum vegetans* (so-called *Pemphigus vegetans*) a distinct specific disease (see also the completely different histology). The disease often begins with, or leads to blisters in the mouth and on the conjunctiva, a complication without much significance, which should not lead to the diagnosis of a so-called *Pemphigus conjunctivæ* (a distinct disease of the eye with destruction of the conjunctival sack and leukoma of the cornea, which terminates in blindness).

It is evident that the previous statements on the histology of pemphigus, which relate to the most varied forms of bullous eruption, need scarcely be considered, with the exception of that of Auspitz, since that author presents a definitely limited clinical description of pemphigus: blisters appearing suddenly on apparently normal skin, without previous spots or the formation of papules, at whose base there may be a slight collateral hyperæmia, but no inflammatory condition. Auspitz finds here, like Haight, the seat of the blister under the horny layer at the region of the transitional layer and that the base of the blister is formed of long drawn out prickle cells which are marked with fissures, but show no formation of a mesh-work developed by colliquation. But he speaks of a "complete destruction of the elements of the prickle layer," and explains the development of the blister through a pre-existing "cachectic character of the epithelium," a view to which he was led by the rapidity of the development of the blister and the absence of the signs of inflammation. Neither does Auspitz admit in the blisters he carefully describes, anything but an overfilling of the capillaries, no cellular infiltration around the vessels, and especially no primary, still more no inflammatory changes in the papillary body. According to him we have to do (in his pemphigus) with "an anomalous growth of the epidermis, which shows itself in mechanical separation of the younger epidermic layers in the form of flabby blisters, showing little inflammatory reaction, or in flat indefinitely limited widespread areas (as *Pemphigus foliaceus*, Cazenave)." Auspitz certainly admits for other bullous formations, as for his "erythema bullosum neuriticum," a mixed character; in it he supposes the blister to be partly "inflammatory" and partly "acantholytic." Although the separation, first undertaken by Auspitz, of the pemphigus blisters from the colliquative vesicles and pustules on the one hand, and from the angio-neurotic bullæ (Herpes Iris and Bullous Erythema) on the other, was most important and valuable, he certainly goes beyond the basis of fact in assuming a cachectic character and consequent destruction of the prickle layer.

Weyl agrees with Haight and Auspitz as to the seat of the blister, while Gustav Simon assumed a separation of the whole epidermis, with tearing of the hair follicle (as in hydroagravis). Kaposi is the supporter of the other extreme, in that he believes the cover of the blister "to be formed from the most superficial horny cells." The base of the blister would then be necessarily formed of the basal horny layer, and the blister would be a pure exfoliation one. As a fact, Kaposi lays weight on the "very superficial seat" of the blister, by which it may be distinguished from that of Eczema and Herpes. He says: "In pemphigus only the uppermost layers of epidermis are lost, and however long it last, and however widespread the process is, there is locally

no loss of substance and no scar developes." With this view that of Haight, on the base of the blister, certainly does not correspond, although Kaposi quotes it and seems to regard it as right.

Certainly the view quoted by Ziegler, that in pemphigus foliaceus the corium is laid bare for considerable areas, is not correct; even the supra-papillary prickle layer does not totally disappear, the greater part of the intra-papillary portion always remains, and the "flakes" consist not of dried up serum, but of swollen dropsical epithelium.

Recently Neusser has announced that, in several cases of pemphigus from Kaposi's Klinik, he has found, both in the blisters and in the blood, an increased number of eosinophilic cells. Neusser concludes from this that the eosinophilic cells are, in this disease, not only produced in the bone marrow, but also in the skin. To me it appears only to show that the same irritant which calls forth the exudation of the pemphigus blister acts in a specific, leucotactic manner on the eosinophilic cells.

This review of the views of authors regarding the bullæ of pemphigus chronicus sufficiently indicates the deficiency in our knowledge, a deficiency which I am unfortunately unable from my own examinations to make good. But I have some experience of the ex-foliative stage of pemphigus.

This termination stage of chronic pemphigus is characterised on the one hand by the very great frailty of the epithelium, and on the other, by a marked over-filling of the cutaneous vessels and œdema of the skin. If we commence with the changes in the cutis, which in this stage deserve most attention, we find the dilatation of the vessels is much more marked and extends much deeper than the clinical appearances lead one to suspect. Arteries and veins are, in their course through the cutis, dilated to their maximum, and the sub-papillary vascular net shows dilatation of all the capillaries, so great as almost to reach the condition of angioma. The papillary vessels are also dilated and almost completely fill many of the papillæ, but they are not so much twisted as is often the case in psoriasis papules, and are not so much affected as those of the sub-papillary net. The lymph vessels and spaces are also fully dilated; and mostly so at the margin between cutis proper and papillary body, and inside the latter; but here, and still more in the cutis proper, the dilatation of the lymph spaces is much less than that of the lymph vessels, which is exactly the opposite condition to that found in angioneurotic œdema of the skin (Erythema bullosum). The explanation of this is simple: the marked œdematous swelling of the connective tissue does not permit any great degree of dilatation of the lymph spaces. The loose connective tissue around the coil glands and the hair follicles, the hypoderm

and fatty tissue (the latter having undergone a colloid change with disappearance of the fat), are especially highly œdematous, and everywhere equally and richly permeated by wandering cells. The firm collagenous network is also swollen, but at the same time more dense, so that the dilated blood and lymph vessels run like canals excavated in a hard tissue. There appears here to be a transition to hyalin or colloid metamorphosis of the collagenous connective tissue, which more frequently accompanies long-standing inflammations. The collagenous tissue also is, in its spaces, permeated with a considerable number of leucocytes, while connective tissue cells with much protoplasm are few.

The changes of the epithelium may be characterized as œdematous, when the exfoliation process is at its height. During this period the epithelium is being renewed, and at this place one finds a hypertrophic ridge net, containing mitoses, a normal granular layer, and a horny layer of varied thickness, which only differs from normal in that all the cells above the basal horny layer show definite signs of nuclear remains, are larger than normal, and by their staining capacity prove themselves to be slightly œdematous and swollen. Where greater hyperæmia has led to exfoliation of this newly-formed horny layer, we have the epidermic picture characteristic of *Pemphigus foliaceus.* The ridge net is again flattened and diminished in size by the swelling of the papillæ, the supra-papillary layer is reduced to a minimum, so that the very much changed horny layer runs close over the heads of the œdematous papillæ. The inter-spinal spaces of the prickle layer are here and there dilated, and contain wandering cells, but a more striking sign of the œdema is the soft character of the epithelium in general, which has as its result—corresponding to the compressed epithelial clumps inside blisters and pustules—that they are deformed by every external pressure, the prickle borders and the inter-spinous spaces disappear, and the appearance is that of a homogeneous mass, containing free nuclei. Over the thus deformed, but still only excessively softened epithelial ridge net, there are only two or three rows of softened and superficially dried, stretched prickle cells doing their best to cover the skin; the horny layer is completely absent. Where, on the contrary, the hyperæmia and the œdema of the prickle layer is less pronounced, there still adhere to the surface, crusts of considerable thickness, which externally consist of softened horny layers, and internally of still uncornified but already flattened layers of prickle cells, richly beset with wandering cells. The thickness of this crust is less to be referred to repeated layers of exudation than to the swelling of the epithelium itself.

Similarly swollen are the epithelial cells of the coil glands deep down in the skin, that of their ducts less so. The epithelial covering

of the follicles after long persistence of Pemphigus foliaceus partly disappears, as do the hairs, but is regenerated if improvement sets in, as is the growth of hair, since remnants of it are everywhere preserved.

One may define the changes which accompany the clinical transformation into *Pemphigus foliaceus*, as a persistent vascular paralysis of a high degree, with dilatation, especially of the sub-papillary lymph vessels, and an œdematous swelling of the constituents of the skin, more firm in the case of the connective tissue, but associated with softening in the case of epithelial elements. The latter leads, on the surface, to the formation of voluminous deciduous scales, which counterbalance the continual new formation of epithelium.

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(*b*). Leuco-serous and Sero-fibrinous Inflammations.

*Cheiropompholyx.**

An eruption of deep-lying, sago-grain-like vesicles on the hands, more rarely on the feet, which, in those disposed to it, persons who sweat readily, usually recurs in summer.

* I prefer Hutchinson's name to that of Tilbury Fox (Dysidrosis) because the lesions are not sweat cysts, and to the shorter one, "Pompholyx," of Robinson, since this affection is limited to the hands and feet, and we can use the name Pompholyx as a general definition.

In the slightest cases only the sides of the fingers are affected, and there the vesicles appear, with slight itching, in a few hours, *transparent rings having been for some time visible around the sweat pores* (Tilbury Fox, Crocker). In more severe cases the whole surface of the hands, which is covered with thick epithelium, and usually also that of the feet, is affected on both sides; where the case is still more severe, the rest of the skin of the hands and feet also suffers. In these cases the vesicles, usually only the size of a pepper-corn, may reach that of peas or plums, and there is then usually added to the condition an acute secondary eczema of the arms, legs, and rest of the body. Cheiropompholyx is distinguished from acute eczema by the fact that even where all the vesicles run together, and there is great swelling of the hands, all redness is absent, that the vesicles never rupture, but dry up spontaneously within fourteen days, and leave behind them no moist softened, but a dry surface, which, after the crust which had formed has fallen off, appears only slightly red.

The histology, and therefore the view of the pathogenesis of this affection, has hung for a long time between the two extremes of sweat cyst (hence the name dysidrosis) and inflammatory vesicle. The earlier observations of Crocker appeared to confirm the sweat cyst theory of Tilbury Fox, as opposed to the theory of inflammatory development of Hutchison. Since then, however, the absolutely corroborative observations of Robinson on the one hand, and Santi and Williams on the other (these last two worked in my laboratory), have definitely proved that the vesicles do not depend on dilatation of the sweat pores—that is, the intra-spinal section of the coil duct. In particular, the very careful examination of Williams on three pieces of skin, with 229 serial sections, have demonstrated the independence of the vesicles of the sweat pores.

Certainly the vesicles very often lie quite close to the sweat pores, but these are pressed to the side, often diminished in size, and form wide loops around the former. And thus the more or less *alkaline* reaction of the contents of the vesicle is no more remarkable but self-evident; we have to do with inflammatory vesicles of a special sort.

The youngest vesicles, whose diameter corresponds to about the breadth of five to ten epithelial cells, lie almost directly underneath the basal horny layer, which at this place, immediately over the vesicle, has suffered a breach in its continuity, in that one or two of the basal horny cells are torn, have their free corners turned outwards, or have partly fallen into the cavity of the vesicle. The contents of the vesicle consist at this stage of a moderate number of leucocytes and clear fibrinous exudation. The fluid presses the adjacent cells of the uppermost rows of the prickle layer and the granular layer asunder; at first there still remain a few epithelial cells, drawn out like cords and plates, with wing-like processes, then these are pressed flat on to the wall of the vesicle, which, the more it grows, becomes the more circular. The further increase is always in an outward direction, for

the thick horny layer of the palm of the hand admits of no stretching. When the vesicles have reached clinically the appearance and the size of boiled sago grains they are found microscopically to fill almost the whole extent of the prickle layer, of which only a small, very much compressed band remains: the base of the blister. The *lateral* cells of the vesicle are formed from the œdematous, horizontally compressed prickle layer which, except for the change of shape of the epithelial cells, the dilatation of the lymph spaces, the presence of fibrinous *spirals*, and a small amount of leucocytes, is otherwise sound, and in no way degenerated. The cover of the blister consists of the œdematous swollen basal horny layer which regularly presents over the centre of the vesicle the lesion of continuity above referred to, with crumpling up of one or two sets of basal horny cells. This opening on the cover of the vesicle leads frequently into a roomy, horizontal, flat cleft in the super-basal horny layer, which is filled with leucocytes and fibrin from the vesicle.

In place of a larger cavity there is sometimes found a communicating system of fine clefts in the super-basal layer, which may be demonstrated by appropriate staining, and indicates a pathological change of the deepest horny layers exactly over the centre of the vesicle. (Fig. 4.)

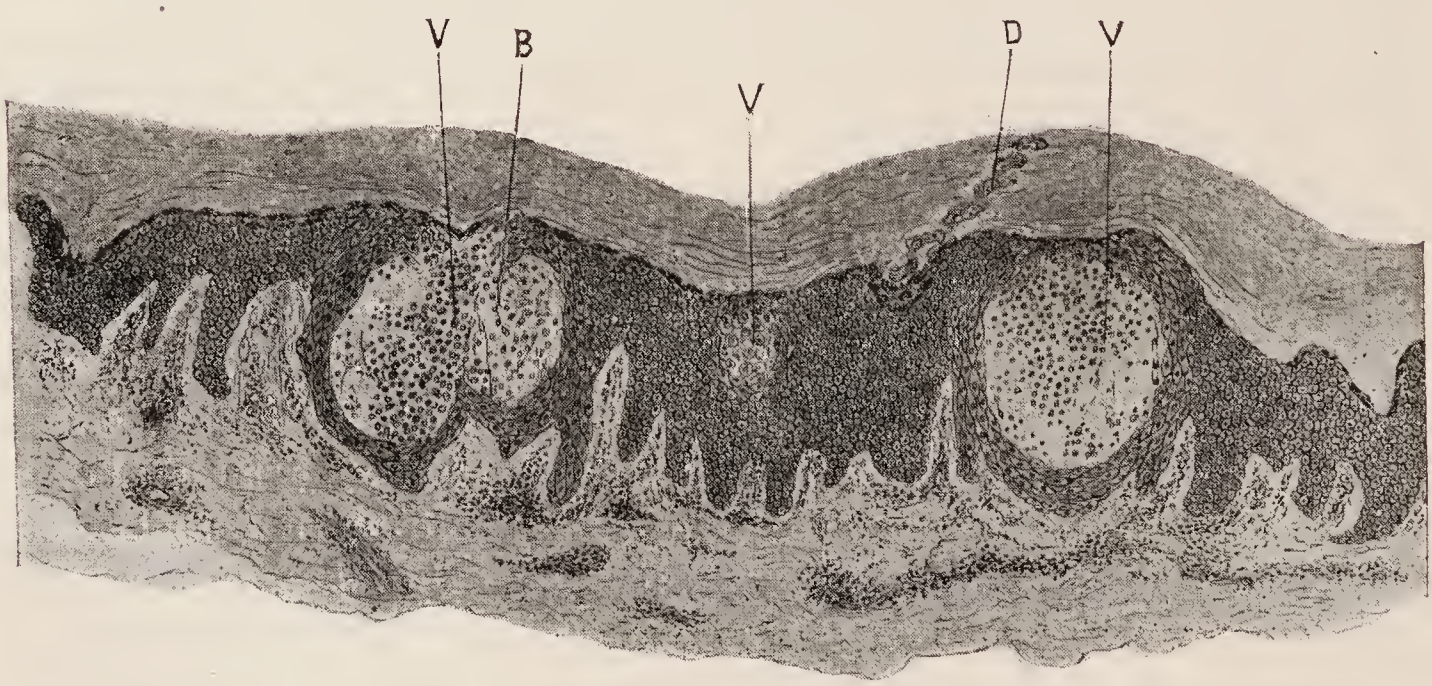

FIG. 4.—Cheiropompholyx. Drawn from Williams' case.

V. Vesicles. *B.* Bottle-shaped opening into horny layer. *D.* Sweat duct.

This invariable *bottle-neck-like* projection of the cavity of the vesicle into the super-basal horny layer, through an opening in the basal layer, is of great importance in the explanation of the process. One cannot regard it as a rupture of the cover of the blister from the pressure of

the exudation, for that never takes place in any vesicle where the horny layer is unchanged, no matter how thin and fine it may be, and certainly not on the thick horny layer of the hand. A softening by means of a histolytic exudation must always be the first stage, if the horny layer yields to the vesicle. But the vesicle of *Cheiropompholyx* never shows any signs of histolysis; it is a simple accumulation vesicle, without trace of co-liquidation or degeneration of the epithelium. The *erosion* of the basal horny layer cannot then take place from inside, from the vesicle, but it must come from outside; the primary affection of the basal horny layer must precede the appearance of the vesicle.

Now, I really believe that I have found here the cause of Cheiropompholyx in a particular bacillus. These bacilli are found both in the super-basal ante-chamber in the cover and in the exudation in the vesicle, partly single, partly arranged in twos and fours. They are best demonstrated by the iodine method. They are about the same length as tubercle bacilli ($2\frac{1}{2}$ to $3\frac{1}{2}\mu$) but are broader ($\frac{1}{2}$ to $\frac{2}{3}\mu$). Very often they lie in twos and threes behind each other, and form zig-zag threads 6 to 8μ long. In the exudation they are only found singly, embedded in fibrin, but on the cover of the vesicle and on the loosened basal horny cells they are found in groups of 4 to 6 bacilli. In comparison with the staphylococci of impetigo they are only present in small numbers, and must, therefore, have a powerful chemotactic action. Their constancy is remarkable; I have been able to demonstrate them by appropriate staining in all the vesicles remaining from the sections of Santi and Williams' cases. In addition to well-formed rods, one finds, in the vesicles, ovoid structures of the same length as the bacilli, and about twice their breadth, which also stain with the gentian iodine method, and which I am inclined to regard as swollen, dying bacilli. I could find no other organisms. In addition to the constancy of the bacilli in the vesicles of two different cases, their presence in the super-basal horny layer on the summit of the vesicle is in favour of their pathological significance.

The pathogenesis of the affection may be thus surmised. In the thick horny layer of the palm of the hand of certain individuals, definite pathophoric bacilli lead a latent existence. The increased sweating in summer or in the course of certain diseases is necessary to induce their proliferation, and this is naturally most active in the neighbourhood of the sweat pores. Here there ensues a maceration of certain basal horny cells, and then rapidly, if the part is scratched, suddenly, a chemotactic setting-free of fibrinous exudation with a few leucocytes. The organisms disperse themselves in the vesicles, which increase until the bacilli, after about a week, die; the vesicle is then encapsuled

by a new horny layer, and thus one attack of Cheiropompholyx is ended.

Such a view of the pathogenesis explains the apparently opposing views of Fox and Crocker on the one hand, and Robinson and Williams on the other, in that the exudative nature of the vesicle is made clear, while its relation to hyperidrosis, and to the neighbourhood of the sweat pores is verified and explained.

The vesicles of Cheiropompholyx present the most perfect example of chemotaxis, in that the dilatation of the superficial capillaries is only evident histologically in minimal degree, and not at all clinically. The migration of white corpuscles is also very slight, and diminishes during the process, so that only the uppermost parts of the vesicle usually contain leucocytes, while the later developed, deeper, and lateral parts contain hardly anything but granular fibrin. That this arrangement is also present in the older vesicles is evident from the rapid coagulation of the greater part of the vesicular fluid. It is chiefly fibrinogenous substances which are drawn from the blood. In the cutis one finds neither fibrin nor leucocytes, but the lymph in the epidermis is very rich in fibrin (Williams). The papillary body is mechanically flattened at the seat of the blister, but otherwise unchanged. In the neighbourhood of the blister, mitoses are present in the epithelium. The encapsuling of the blister and the separation of the crust take place in the ordinary manner.

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Miliaria rubra et Alba.

We place Miliaria immediately after Cheiropompholyx, because, like that affection, it is accompanied clinically by hyperidrotic conditions of the skin. It appears always in the form of small, just recognisable vesicles upon reddened miliary papules, and always superficially over large areas of the body. When these do not immediately dry up, they increase, and then may be definitely recognised as white points on the red papules. Very frequently the miliaria vesicle forms the starting point for acute infectious catarrhs of the skin, which spread over the whole body, especially for seborrhœic eczema.

Although up to now no specific organism has been recognised * in miliaria, we must regard it as of parasitic development, on account of the whole structure of the miliaria vesicle, which is closely related to that of Cheiropompholyx and of acute eczema. It is, like those, an

* Only in one section of Miliaria did we find a bacillus, using the Iodine method.

acute vesicle, formed chemotactically in the epidermis. Now, such a chemotactic action is always conceivable as the effect of some substance excreted in the sweat. But such could never be in the position of causing the exquisitely punctiform exanthem of miliaria, but would induce a more diffuse irritation, for the sweat spreads itself diffusely in the horny layer.

In the earlier anatomical statements regarding Miliaria there is great confusion, in particular, because Crystallina,* quite a different affection from Miliaria, has evidently been confounded with it, and has been described in its place. Crocker agrees with the view of Haight and Robinson, that in Miliaria the blister is found inside the horny layer, and is filled with sweat; all these authors were probably examining Crystallina vesicles. Kaposi regards the vesicles "as the result of the collection of sweat between layers of epidermis filling (?) the mouths of the sweat glands," without explaining what peculiar form of enclosed horn he means. But Neumann gives the following explanation: "of the development of Sudamina, it is only known that inflammatory exudation collects between epidermis and cutis (!); that thus stagnation of the sweat in the dilated openings of the glands ensues, is more than probable; a collection of sweat takes place between the lamellæ of the epidermis (Haight)" regarding them first as sub-epithelial inflammatory blisters, then as sweat cysts of the pores, and finally, thirdly, as intra-corneal collections of sweat!

Török has proved in my laboratory, on excised vesicles of *Miliaria rubra*, that we have to do with inflammatory vesicles of the epidermis without any relation to the sweat ducts, and that this is only to be found in Crystallina. From his and from later excised material I can thoroughly corroborate these statements. The vesicles begin, like those of Cheiropompholyx, in the basal horny layer, with the dilatation of certain inter-epithelial spaces, and rapidly extend to form large monolocular blisters, which occupy the whole thickness of the prickle layer. The prickle cells are pushed to a side and compressed, and only a very thin layer of compressed prickle cells remains as the base of the blister. The horny layer forms the cover of the blister; some of the adjacent horny cells are softened, loosened, and mixed with the contents of the blister; but a large superbasal cleft, with rupture into the blister, as in Cheiropompholyx, does not exist here; the undermost non-fatty portion of the basal horny layer is from the commencement separated from the upper fatty (blackened by osmium) part, and remains in contact with the underlying epithelium.

The contents of the blister consist of granularly coagulated serum without the admixture of fibrin, in which a sometimes large, some-

* The erroneous term "Miliaria crystallica" should be abandoned.

times moderate number of mono- and poly-nuclear leucocytes, single epithelial cells, and a good many large, round, peculiarly granular cells are suspended. The granules of these latter greedily take up anilin colours and retain them in the presence of acid: they are therefore mast cells. Indeed, one always sees in the dilated lymph spaces of the wall of the vesicle, in addition to a few leucocytes, a not inconsiderable number of mast cells at the border of the cutis next the vesicle. This chemotactic attraction of mast cells the Miliaria vesicle shares with certain carcinomatous epithelial growths. In osmium preparations some granules of these wandering mast cells take a black stain (fat granules). (Fig. 5.)

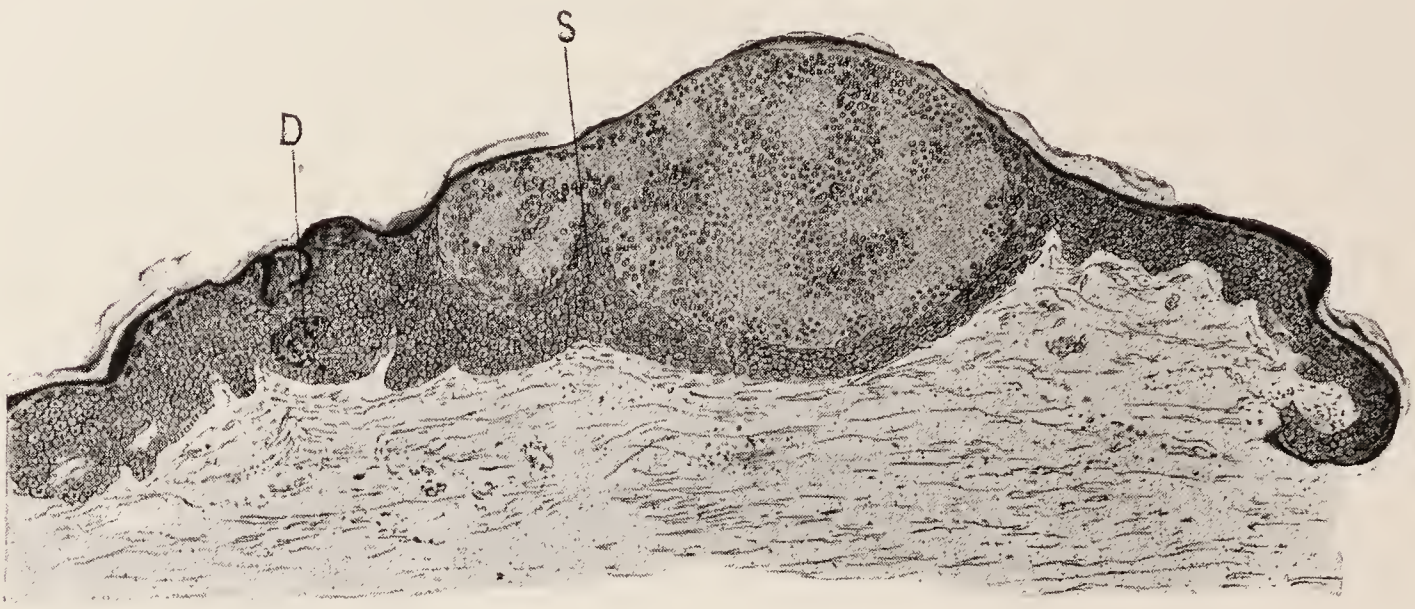

FIG. 5.—Two Miliaria vesicles.

S. Septum partially persisting between them.

D. Sweat duct. The vesicles contain epithelial cells and leucocytes.

Where two miliaria vesicles, by their concentric increase, run together, there is only a compression, not a softening of the epithelium lying between. There develope, then, larger vesicles, having the form of hour-glasses, into which the remains of the previous dividing wall project like spurs. The vesicle may also come into contact in this secondary way with sweat pores: primary connection with them and a development from them must be completely excluded.

The appearances of inflammation in the cutis are very slight, and are limited to a dilatation of the superficial capillaries, and a very moderate migration of leucocytes from the vessels, and of mast cells from the cutis, into the epithelium. The pathological changes of the neighbouring epithelium consist in more or less widespread inter-epithelial œdema, and in the presence of scattered leucocytes, mast cells, and a few mitoses. A diffuse parakeratosis, as in eczema, does not exist in Miliaria.

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Impetigo, Impetigo contagiosa.

The eruptions of the skin described as impetiginous, appear especially in children, and form yellowish, yellowish-green, or yellowish-brown crusts, under which a sero-purulent fluid usually stagnates, and wells out when the crust is removed. These are sometimes found alone, single, or grouped, sometimes in combination with diffuse widespread eczemas, especially of the head. They were consequently all grouped together, along with eczema, by the older Hebra: he did not recognise Impetigo as a special disease. When the significance of parasites for disease in general, and especially for purulent diseases, became known, it was very easy to assume, as was done by many, that these "impetiginous eczemas" were mixed forms of eczema plus the action of the ordinary pyococci. The work of Bockhart first taught us the true form of the impetigo caused by the ordinary pyococci, and from this it was evident that the much more numerous cases of impetigo, especially in out-patient children's practice, did not belong to it; and it is therefore necessary, specially to indicate Bockhart's impetigo, as well as the true staphylogenous epidermic abscess (see that), as Impetigo staphylogenes.

Now it would perhaps have been well, and certainly consistent, to have reserved the name impetigo for the, at that time, best understood pustules of the skin. But this appeared impossible, first, in view of the everywhere accepted meaning—impetiginous eczema for purulent and crusted eczema; and then, because a disease, thoroughly distinct from eczema, had already been long known—the *Impetigo contagiosa* of Tilbury Fox—which was nearly related to this impetigo-like eruption, and whose name was firmly established.

But if we retain the name of impetigo, both for certain crusted eczemas and for the impetigo contagiosa of Fox, it must consequently be applied to all those acutely appearing exanthems, *which consist of discrete or grouped superficial vesicles and blisters, which rapidly turn into crusts, and when these are thrown off, heal without scars.* These form a large proportion in out-patient practice among the poor, and are by no means all alike. As they are all more or less contagious, and usually affect several children in a family, it is very difficult to separate them from impetigo contagiosa proper. But it would be well to reckon as these, only those eruptions which appear in small epidemics in schools, in many children of neighbouring families, or after public vaccination, and thus indicate their *specially easy* communicatibility.

If we were to find out that, along with this specially severe contagiousness, there were also certain clinical characteristics, and were a definite organism found in these cases, the definition of Impetigo contagiosa should be retained for this *specially contagious form*. I have no material for examination from cases belonging to great epidemics; so far as I know, none of them have been thoroughly investigated histologically. The bacteriological discoveries of the older authors are no longer of any value, and even those attained in the Rugen epidemic of 1885 did not lead us to the knowledge of the actual cause of the disease.

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Of the distinctly less contagious impetigines which are constantly present in the children of poor districts, there are, in my experience, two distinct clinical forms, of which the one is very much commoner than the other. They are distinguished by the fact that the first forms thick voluminous crusts, which, by their contact, assume polycyclical forms, while the second shows thin crusts, which increase themselves by concentric extension. The first I have called *impetigo vulgaris*, the latter *impetigo circinata*. The first is frequently combined with eczema of the head, and is probably a mixed infection of seborrhœic eczema, and this widespread form of impetigo represents the chief contingent of the so-called "impetiginous eczemas" of children, while it is notorious, that, during the presence of eczema, a true staphylogenous impetigo cannot find a seat, and only appears as post eczematous impetigo and furunculosis.

Still rarer, and only seen in a few cases, are the purulent and fibrino-purulent forms of *impetigo streptogenes*, *impetigo multilocularis*, and *impetigo fibrinosa*, which are allied to staphylogenous impetigo.

And so the definition of impetigo is necessarily gradually widened, by the knowledge of a great series of crust-forming vesicular diseases like the true staphylogenic impetigo, from the special one of the pustule to the general one of the *infectious crust-forming vesicular* diseases. In this connection I have already described certain histo-

logically most interesting, although clinically rare cases of serous and leuco-serous vesicles at the commencement of the chapter as *impetigo serosa* and *impetigo protuberans.* From eczema all these impetigines differ chiefly in this, that they induce *no superficial, diffusely spread disease of the epidermis in addition to the vesicles; they have always a limited character, and the eruption limits itself to scattered or grouped isolated vesicles and crusts.* By the ever-widening knowledge of this large group of infectious moist catarrhs of the skin, Eczema, Pemphigus and Ecthyma, will undergo some limitation.

Impetigo Vulgaris.

This most frequent form of the impetigines leading to fibrinous crusts, affects usually the faces, especially the region of the mouth and nose, of children of poor nutrition. The vesicles are small, usually localised in a follicle, and are rapidly converted into crusts, which attract attention by their thickness and greenish-yellow colour, and by the constantly exuding secretion are converted into thick scabs, the size of a pea to a lentil (1, 2, 3 mm.). These are loosely adherent, are often scratched or knocked off by the children, and are quickly replaced by new yellowish-green or yellowish-brown scabs. By their concurrence there develope on the seats of predilection, masses of polycyclical crusts the size of half-a-crown. In addition to the face, these groups of impetigines are found on the hands, the hairy scalp, the arms, legs, and buttocks; more rarely on the back. After about two weeks the crusts fall off, leaving behind them red spots but no scars. During this period the affection spreads by fresh inoculation, and is usually, if not medically treated, of long duration. From *impetigo staphylogenes*, *impetigo vulgaris* differs in the fibrinous nature of the crust, the absence of marked suppuration, and in the localisation; it never leads to the formation of furuncules. From crusted eczema, impetigo vulgaris can be separated, by noting that the latter always appears in discrete spots on otherwise healthy skin, the former spreads diffusely and passes into other forms of eczema.

In order to secure the vesicular stage of *impetigo vulgaris*, one must excise the first little red point, in the neighbourhood of the crusts, which shows on its apex a just perceptible vesicle. If one waits until this is increased to a distinct vesicle, one only obtains crusts, *i.e.*, vesicles already in process of healing, so rapidly does the vesicular stage of this form of impetigo pass. Here one finds, centred around a hair follicle, marked changes of the cutis and epidermis. The papillary body and the cutis round the hair follicle neck are œdematous, permeated by wide lymph spaces; the blood vessels of this region are dilated, as are the lymph spaces round them, and the perithelia are increased; but the leucocytosis from them is slight or altogether absent. The prickle layer in the neighbourhood of the follicle, and that of the hair follicle neck, are in their under part also markedly œdematous. The prickle cells are here compressed to fine cords or stellate cells, by the marked distension of the inter-spinal lymph tracks. At many

places the gaping lymph spaces of the papillary body directly communicate with those of the epidermis. Except for the compression, the prickle cells suffer no other changes; their protoplasm and their nuclei are well stained. The upper part of the prickle layer is less œdematous; the dilatation of the lymph spaces here gradually ceases, and the cornification on the surface round the follicle is not disturbed. Certainly the uppermost horny layer is not elevated, as the name of impetigo would lead us to expect. If we search further, whence this fibrinous exudation which is seated at the follicle neck, and is clinically evident as a conical vesicle, really comes, we learn, that a communication between the œdema spaces of the prickle layer and the follicle neck only exists at the bottom of the follicle neck. As a fact, there exists an inter-cellular cavity formation through the whole thickness of the prickle layer, and a formation of larger cavities, true vesicles, only where the prickle layer dips into the hair follicle. Here exists, then, a larger vesicular space, filled with serous, later fibrinous exudation, in which the hair is pressed pretty far from the œdematous prickle layer of the follicle neck. From here the exudation makes its way, by softening the horny layers which fill the follicle neck, to the surface, and elevates the horny layer, which horizontally covers the follicle, in the form of a conical vesicle.

The meaning of this peculiar deep formation of the vesicle is very clear, if we follow the micro-organisms and note that these have everywhere grown along the hair shaft down to the bottom of the follicle neck.

They are elongated oval cocci ·8-1μ in size, and present no marked differences in size, like the morococci of eczema. Their arrangement is irregularly clustered, like that of the staphylococci. From these they are distinguished even in the vesicle, since they attract no leucocytes, but a pure serous exudation. Only this one form of micro-organism is found in the epidermis.

From these observations it is easily understood how it is so difficult to find the primary vesicle of *impetigo vulgaris*, and to follow it in its development. The commencement of the exudation does not take place on the surface, but in the prickle layer of the hair follicle neck, which the cocci have reached. Here there takes place the powerful serotaxis, which leads to a pretty pronounced perifollicular œdema, and, further, to the formation of vesicles in the mouth of the follicle, and to free exudation in the neck. Here there forms, from a few horny lamellæ and much serous exudation, a crust, which at once coagulates, and by its superficial position under a thin horny layer presents slight resistance to further exudation. It increases rapidly up to the size of a pea, and in it the cocci find a congenial soil, and multiply very rapidly. It

consists only at its borders of horny layer, the whole of the middle is occupied by a relatively soft fibrinous clot, through which the cocci grow in long rows. Here and there they form larger collections, which give off branching processes. They have no tendency to form compact packets and regular figures. In the larger collections these cocci present no regular type (like the morococci) but here also rather resemble the staphylococci. It must, however, be noted that with the iodine method they very often present in the centre a colourless part, so that only certain marginal parts of the cocci stain deeply: this appearance may indicate a rapid death of the cocci (in the morococci of eczema I have never met with this appearance).

If the crusts are allowed to run their course spontaneously, the skin underneath them, when they fall off, although thin, is already cornified. But it is otherwise when the crusts, as is usually the case, are removed by scratching. Then the horny layer in the neighbourhood of the follicle is torn with them, and thus an artificial erosion of larger extent is produced. The epidermis now assumes an eczematous appearance, and the differential diagnosis is made more difficult; for naturally the exudation uses the newly provided, raw surface, and the formation of crusts extends not only superficially, it extends deeper into the epidermis, and is more adhesive than at the commencement; but there is never developed the characteristic persistent parakeratosis as in eczema, and generally, in contrast to eczema, impetigo vulgaris tends to rapid healing.

Impetigo circinata.

In contrast to impetigo vulgaris, impetigo circinata forms flat, thin crusts, which sink in in the middle and spread at the margin. The following relates to a typical case of this variety in an old man :—

A. L. for eight days has had an eruption of vesicles on the face, in the neighbourhood of the mouth and nose, chin, forehead, cheeks, and in the beard. Most of the blisters have become converted into flat, brownish crusts which extend peripherally, while they sink in in the centre and scale. A perfectly fresh serous vesicle showed a slight, red halo. A recent vesicle with commencing central crust formation was removed.

Central sections through the spot show the epidermis in the centre flattened, as compared with the margin. In both places the prickle layer is very œdematous, partly through swelling of the cells, but chiefly through inter-cellular œdema. But while at the margin the horny layer is elevated by it, and there are, at some places, large inter-spinal vesicles, in the central part the inter-spinal exudation is completely coagulated and stains like fibrin. As it contracts, there is formed, from the upper prickle layer and the horny layer, a thin crust, in which the diminished nuclei are entangled. The central depression

therefore ensues, because the crust begins, not above but inside the prickle layer, and is seated directly on the under part of the prickle layer, which, in spite of the œdema, is diminished. The rapid coagulation of the serous exudation is possibly the cause of the organisms wandering into the peripheral, simply dropsical part, and thus leading to the centrifugal spread of the eruption. There is found only one definite variety of coccus, which differs from the cocci of *impetigo vulgaris* by its perfectly round form. Further, the collections are more regular, sometimes like the mulberry forms of morococci, but usually more angled, almost cubical. In the young vesicles they are in the form of double and quadruple cocci, with smaller collections in the crust and the peripheral horny layer. In the older crusts they multiply and then sometimes show an enormous collection of the peculiar, angled colonies just described. The single cocci measure ·7 to 1μ, but the larger collections show some measuring 1·25μ, which, in spite of their round form, are to be viewed as cocci about to divide, but not yet divided.

In two other cases of impetigo circinata which affected children, I found, in the crust, apparently exactly the same large angled packets, consisting of cocci of a round type.

The changes in the cutis are limited to a moderate œdema, dilatation of the blood vessels, increase in number and size of the perithelial cells, and a slight leucocytosis.

Impetigo streptogenes.

The pustule, got from the corpse of a child, differed from the ordinary staphylogenic impetigo macroscopically in its lighter and less greenish-yellow colour, its greater flatness, and its irregular form with numerous processes.

The vesicles are single chambered, very large and roomy, and the elevation of the horny layer extends more widely microscopically, than its macroscopic appearance suggests. It extends into the neck of the hair follicle which runs through it, and in many places insinuates itself between the papillary body and the epithelium. The cover of the blister consists, as in staphylogenic impetigo, simply of horny layer, which has here become more yielding, and is therefore very much folded. The base of the blister is, however, quite different; the prickle layer is much loosened on its upper surface, broken down into numerous epithelial balls, which are mingled with the contents of the vesicle, and in many places it is completely loosened from the papillary body, and floats free in the vesicle. This solution is facilitated by the œdema and swelling of the papillæ, so that the papillary body is not flattened and smoothed out as in staphylogenic impetigo, but, on the contrary, is

swollen, and, partly covered with prickle layer, projects naked into the pustule.

The cutis also, underneath the blister, gives evidence of being conjointly affected. It is œdematous as far down as the sub-papillary vascular net, the lymph spaces are dilated, and, as in erysipelas, although in much less degree, the collagen is especially attacked. In double staining with orcein and orange, certain stretches of the collagenous bundles take up the yellow stain, so that the bundles of fibrils, as a whole, appear piebald or even worm-eaten. The elastin inside the papillary body has partly disappeared and is only faintly stained.

The contents of the blister consist of much serum with a moderate amount of leucocytes, and almost as many loosened uncornified epithelial cells and epithelial collections, all mixed together. But the most important element is an enormous quantity of streptococci, which, in the form of small rows of 6 to 10 individuals, or as diplococci, more rarely in coil-formed longer twisted rows, or in the form of layers spread on the surface of single epithelial cells, swim mostly free in the pus (droplet), and are pretty equally distributed through it. They are found likewise in rows on the upper and under surface of the cover of the vesicle, extend, in the sub-epithelial spaces, into the depths of the inter-papillary grooves, and further, deep into the space between the prickle layer and the root sheath of the hair follicle. I have not found the streptococci in the connective tissue of the cutis and the papillary body. It is a characteristic fact that, in the vesicle, they are not found inside the leucocytes, which indicates their vigour and vitality; the streptococci of erysipelas are only taken up by leucocytes when they (in the hypoderm) are dying off in numbers. The entrance point of the streptococci appears to be the horny layer of the hair follicle neck, from whence, through fine tears, they reach the prickle layer of the surrounding epidermis.

If we compare the characteristic microscopical features of this streptogenic impetigo with the staphylogenic impetigo, we must lay most stress on the lesser leucotactic and much greater serotactic action of the streptococci, on their rapid and wide-spread distribution through the whole vesicle, and on the histolytic action of the tissue juices, which is indicated in the alteration of the collagenous tissue, and the ready separation of the epithelium. The greater flabbiness, the smaller amount of pus, the undetermined margin of the vesicle, and the œdema of the papillary body are further effects of these primitive qualities of the streptococci and of the exudation they set free.

The eruption just described had evidently appeared shortly before death, from an unknown infectious disease. From what we know of the qualities of the streptococci, an attack on the cutis, with erysipelas-

like symptoms, would certainly have ensued had this impetigo lasted any time. I have a piece of skin from the nose of a fatal case of erysipelas, where, in addition to the already existing general infection, the cocci had attacked the skin through the wounded epidermis. The entrance of the streptococci into the skin from an epidermic abscess (in contrast to staphylogenic impetigo) is certainly much rarer than that through fine tears of the surface of the mucous membrane (especially the nose).

Eczema.

I. *Acute vesicular eczema (inoculated eczema).*

Of three sisters M. all affected with seborrhœic, squamous, partly psoriatiform eczema, the younger ones had, in addition, impetigo-like scattered vesicles on the face and hands, which were distinguished from the true staphylogenic impetigo by their lighter yellow (less greenish-yellow) colour and their broader inflammatory halo.

A vesicle, the size of a mustard seed, of a yellow colour and surrounded by a red halo, showed, on section, a flat base, consisting mostly of prickle layer, over which the cover of the vesicle, consisting of horny layer and a few adherent, swollen, epithelial cells, was semispherically elevated. The contents of the vesicle were about one quarter leucocytes and three quarters fluid and coagulated serum, without any admixture of fibrin. A considerable number of detached, partly ballooned epithelial cells floated free in the contents of the vesicle. Under the middle of the cover, and inside a hair follicle which ran through the vesicle, there were collections of the morococci of eczema, sometimes in rows of diplococci, sometimes in the form of older, mulberry-shaped packets. Scattered all through the contents were found, either enclosed in leucocytes or adherent to them, well-stained morococci of varied size, but almost all in the form of diplococci.

The cutis underneath the vesicle was also characteristically altered. All the cells, but especially the perithelia of the blood vessels, as far down as the deeper vascular net, were swollen and increased; here and there mitosis was evident. There were no plasma cells, and mast cells were present in no more than normal amount. All the lymph spaces and the blood vessels were moderately dilated. The papillary body was not depressed, evidently the swelling of the cutis counterbalanced the pressure of the vesicle.

The prickle layer underneath the vesicle shows a considerable dilatation of all the lymph spaces, and consequently the prickle cells, although they are swollen, appear, especially in the under layers, to be markedly diminished in size. Compared to the considerable amount of

serum, the number of leucocytes which are present in the base of the blister is not great. The epithelial cells, surrounding the blister, participate to some extent in the œdema. Here, and in the epithelium of the base of the vesicle, we find a striking number of mitoses, as also in the prickle layer of the hair follicle which traverses the vesicle.

The inter-epithelial œdema leads to a loosening of the upper layers of the base of the vesicle, and single epithelial cells and collections of them are mixed in its contents. The cover of the vesicle also is not sharply margined, but is partly loosened and covered on its under surface with loosened and rounded horny cells; sometimes there adhere to it swollen and ballooned fragments of the prickle and granular layers.

Œdema and hyper-nutrition, with formation of mitoses in the surrounding cutis and epidermis, an exudation more serous than leucocytic, not sharply marked off from the loosened, vesicular walls, swollen epithelial cells and leucocytes containing morococci in the monolocular vesicles, morococci on the surface and under side of the swollen, horny layer—these are the symptoms which are present in the acute eczematous vesicle and definitely characterise it.

The bacteriological examination of the different forms of vesicle, which may be present in eczema, first led us to definite conclusions on their relative relations and their etiological connection. The better comprehension which we thus attain even of the clinical relations of eczema, and the possibility of a very simple demonstration of the whole pathology of eczema based upon it, are two fresh indications that these given etiological factors are the ones which alone are to be considered.

From the bacteriological side, we have to distinguish two thoroughly distinct varieties of eczema vesicle. The **first,** just described, is very like that of staphylogenic impetigo, and constitutes, like it, the only pathological change in the skin. Here it is the bacteria—the morococci of eczema—whose invariable presence in the vesicle alone enables us to recognise it as a form of eczema.

The **second** form of eczema vesicle is much more multiform, and is not the only change in the skin, but rather appears in addition to other long-developed and characteristic eczematous changes of the epidermis. These vesicles do not develope by the sudden penetration of the morococci into the prickle layer, but by the ever-increasing congestion of leucocytes and serous transudation, which strive to reach the *horny layer*—in this case, the situation of the morococci—but are held back by the transitional layers. They contain, then, in general, no morococci, although, in exceptional cases, where the vesicles have a long duration, *single* cocci may reach them.

The **former** vesicle represents the condition which is alone rightly

termed "acute vesicular eczema," * or better, "the primitive acute outbreak of eczema in the form of vesicles," which, as such, rapidly heals or passes into the ordinary common eczema, that is, a chronic skin disease.

The **latter** represent the acute and sub-acute vesicular patches, which appear during the course of chronic eczema on *parts* of the skin, which are *already eczematous.* They develope less suddenly and last longer.

The **former** are pathologically interesting in the highest degree, but they are by no means characteristic of the eczematous condition of the skin. The morococci have had neither time nor a suitable soil in which to induce that parakeratosis which is characteristic of eczema; they have rather got directly under the normal horny layer by some lucky chance, an inoculation, and act then as staphylococci would in such a case, viz., they induce a sub-corneal, well-defined epidermic abscess. I will linger over this phenomenon in order to show that this acute impetigo-like vesicle still distinctly differs from staphylogenic impetigo.

There are two fundamental differences between the processes, on which all the histological differences depend, one, the attraction of a *purulent* exudation by the staphylococci, and a *scro-purulent* one by the morococci; the other the *different relation* of the two organisms *to the leucocytes.*

The first condition makes staphylogenic impetigo a vesicle with immovable contents; a drop of pus consisting of closely-packed leucocytes endeavours to detain the staphylococci under the horny layer and to prevent their entrance into the prickle layer. At first the attempt is successful, and the staphylococci extend themselves in recent impetigines, superficially, under the horny layer. After they have lasted some time, and the leucocytes have perished, the staphylococci grow radially outwards through the collection of pus, mostly in the form of streaks. Only after very long undisturbed existence is there now and then seen a complete permeation of the drop of pus by staphylococci.

Thanks to the fluid character of the vesicle in the impetigo-like eczema vesicle, the morococci distribute themselves more evenly through it from the very first. One never finds them collected and fixed in a thick layer under the horny layer; indeed they are sometimes found freely distributed all over the periphery of the vesicle. In place of connected streaks and flakes, they form, preferentially, scattered clumps.

* Very different from Hebra's so-called acute eczema, accompanied by erysipelatous inflammation and œdema, which, to my mind, is sometimes simple traumatic dermatitis, sometimes that, plus pre-existing eczema.

While, further, the pus drop of staphylogenic impetigo in most cases consists of leucocytes only, and only occasionally presents a small number of loosened horny cells, the sero-purulent vesicle of eczema always contains a very mixed collection. In particular, we always find here a considerable number of prickle cells, either unchanged or somewhat swollen, and, closely mixed up with the leucocytes, one or two, but relatively few, horny cells. Now and again, in addition to the leucocytes, mast cells are found in the vesicles. All these varieties of cells are much less closely arranged than the pus cells of the impetigo pustule, for they have between them a more or less considerable quantity of serum.

As in the fluid drop, the cellular surroundings are different in the two cases. In the staphylogenic impetigo the whole prickle layer is compressed round about the drop into a firm shell, which is very sharply marked off from the drop of pus. It presents no opening, and so few leucocytes that one can hardly conceive how these have reached the spot; one finds, however, certain open bye-ways, *e.g.*, the coil ducts, filled with them. In the impetigo-like eczema vesicle, on the contrary, the prickle layer immediately around is loosened, it passes by loosened collections of prickle cells gradually into the contents of the vesicle. In place of a general smooth vesicular contour, we usually find, especially above and on the sides, a number of smaller epithelial sub-cavities which partly open into the larger vesicle, and are also filled with serum and leucocytes. The latter are visible in many of the dilated spaces of the prickle layer, and this appears thinned, having contributed many collections of single cells to the vesicular contents. In short, the prickle layer of the surroundings of the vesicle is partly rarefied, loosened, and irregularly arranged.

The horny layer, also, which forms the cover of both varieties of vesicle, does not behave in exactly the same way. There certainly are absent in this acute eczema vesicle the widespread œdematous changes of the horny layer which characterise chronic eczema, and in the pustule of impetigo are always absent, but at a limited spot of the horny covering, in the centre, where the invasion of the morococci has taken place, there is nevertheless found a limited softening of the horny cells. At this place the cover of the vesicle yields more readily, and is often torn in preparation, which never occurs in the staphylogenic impetigines.

In these, as above noted, the horny covering is sharply separated from the drop of pus by a layer of cocci in the centre, while the horny layer of the covering in the eczema vesicle gradually passes in the centre into the vesicular contents, in that, on the one hand, leucocytes and serous exudation penetrate between the loosened horny cells, and

on the other, detached collections of horny and transitional cells are attached to the deeper-lying prickle cells of the vesicular contents.

Finally, there now and again developes in the acute eczema vesicle, as a result of the marked serous exudation, thready and granular coagulation, especially at the base of the vesicle. But I have not been able to recognise (with Weigert's method) any true fibrin, which is always present in the vesicles of chronic eczema. On this point, therefore, in the differentiation from staphylogenic impetigo there is not much stress to be laid; for these latter, when they have long existed, and the action of the poison has diminished, also show the same coagulation at the base of the blister. Nor do we have colliquative changes in the prickle cells. Only the inter-spinal lymph tracks are dilated, and sometimes, around the vesicle, the perinuclear spaces.

The second main distinction in the formation of the vesicles is the relation of the cocci to the leucocytes. The staphylococci appear completely to paralyse the white blood corpuscles in their neighbourhood; these, in spite of their numbers, are no longer able to take up the staphylococci, which, spreading themselves in cluster form, range freely through the pus. It is different with the morococci. These also increase in their characteristic way in the form of mulberry-shaped groups. They do not reach, in the contents of the blister, such a size as in the horny layer; groups of four to eight cocci vary with diplococci, which form most free morococci show. But in addition one finds very many of them enclosed in leucocytes, seldom less than four, usually eight to sixteen, and as many as thirty or more in one white blood corpuscle. Evidently they multiply rapidly in them, and gradually lead, like gonococci, to their death. In favour of this are larger collections of morococci, which surround a leucocytic nucleus, but are enclosed by no film of protoplasm. This enclosure of single diplococci in leucocytes probably acts in the same way as the mobility and serosity of the vesicular contents, leading to a rapid distribution of the cocci all through the vesicle. When we consider that in the staphylogenic impetigo the vigorous and free leucocytes are not able to take up the staphylococci, while in the morogenic vesicles the less powerful and less completely detached leucocytes are, we may well conclude that the morococci are less poisonous to the white blood corpuscles. They attract them less, are readily taken up by them, increase in them, and destroy them, while the staphylococci attract them very powerfully, and when they get near destroy them, and thus the mutual relations are at once arrested.

Since the prickle layer immediately around the vesicles, with the exception of inter-epithelial œdema, presents no noteworthy changes,

healing takes place promptly by simple encapsulation. The depressed base of the vesicle becomes cornified, and a new mitotic epithelial proliferation elevates the whole vesicle. This dries up to a flat button-like crust, which, in its upper part, represents the old horny layer, in its under, the coagulated and flattened contents of the vesicle. The coagulation leads to a loose fibrinoid mass, which only takes a faint fibrin stain with Weigert's method. It is of great importance to note, that in this crust the morococci *proliferate* actively, and one must therefore regard the crust as a good medium of infection. As they always do in dry surroundings, the morococci assume much larger dimensions, exactly as they do in old cultures. A suitable methyl-blue stain analyses these large forms into packets of four, eight, or sixteen smaller ones, and shows that this delayed separation with continuous division leads to this giant coccus form (Klebetheilung).

Having put this acute eczema vesicle * in its proper place, we now turn to chronic eczema proper; the moist catarrh of the skin. After excluding the vesicle, we can treat all other changes of the eczematous skin, however different they may appear clinically, from a uniform point. We have, indeed, in chronic eczema, to do with a uniform histological process, just as with a uniform etiological one. But the unity does not consist, as was long taught, in a constant series of stages, a papular, vesicular, weeping, red, scaling eczema. For eczemas neither go through the same stages, nor do they follow, even when these conditions are present, a given or even a definite series. For example, very many eczemas begin as squamous eczemas, and remain as such; others begin as papular eczemas, and end either so, or as scaling eczemas. Vesicles are usually only an acute complication, &c. The polymorphism of eczema may be rather attributed in a sense to a histological unity, in that a *uniform complex of three histological symptoms* really presents the basis of every eczema, and the multiformity partly depends on this—that the three symptoms are differently developed in every case, sometimes through the addition of definite new complications, still to be described.

II. Chronic Eczema.

The histology of eczema may be limited to the explanation of the simple elementary forms, for the combined elementary forms—the synanthems of eczema—show the same histological changes, only in different arrangement or in different intensity.

* The "inoculation vesicle" of eczema, if we unite that produced artificially by the inoculation of morococci, with the spontaneous, but probably also mechanically-induced one. The histology of both is alike.

Each of the three elementary forms relates to a special histological process, namely—

1. *The scale formation; Parakeratosis.*
2. *The papule formation; the epithelial growth; Acanthosis.*
3. *The vesicle formation; the spongy transformation of the epithelium.*

The altered method of cornification, parakeratosis, alone characterises the mildest commencing forms; but, combined with the other pathological changes, it is found in all the others, even in the highest developments of the disease. Along with the epithelial growth we find parakeratosis in the dry papular scaly, or crusted psoriasis-like forms. Combined with the spongy transformation of the epithelium, parakeratosis characterises the moist, crusted, or simple weeping vesicular forms, the so-called eczema rubrum, &c. But as these three changes are all the necessary results of a distant cause, *Serum-Chemotaxis* (sero-taxis), we may consider them with advantage separately. It will thus not be difficult to construct, from their combined action, both the simple and the combined elementary forms, by adding those changes in the connective tissue and the blood vessels, which are common to all forms, and may be developed in different intensity in any form. Finally, we have certain terminal forms and frequent complications of eczema to consider by themselves, such as the condition of pruriginous hardening, of malignant exfoliation, of rosacea, of hyperkeratosis, of exulceration, &c.

1. *Parakeratosis.*

This anomaly of cornification, which is to be found in all true eczemas, in the simplest forms of pityriasis, as in the severest weeping eczemas and the oldest psoriasis-like forms, which indeed, more than all other symptoms, serves as the histological characteristic of eczema, may be shortly defined as an œdema of the *transitional epithelium*. It is no interstitial œdema, no abnormal collection of tissue juices between the epithelial cells, but a parenchymatous œdema, an increased amount of fluid in the epithelial cells themselves. This gives evidence of its presence, in the prickle layer, by increase in the volume of the epithelial cells, and especially of the nuclei, which become rounder and stain less. The lymph spaces are very well developed and roomy, but not abnormally, and certainly not irregularly dilated. By this parenchymatous swelling of the epithelium, the whole prickle layer of the affected part is rather markedly increased in breadth, and the ridge system "gives" at this place, while the supra-papillary prickle layer often, but not always, extends outwards beyond the neighbouring

normal prickle layer. There exists then, already, a broadening of the prickle layer in eczema, independent of and previous to any epithelial growth.

The larger amount of fluid in the epithelium is indicated especially in the granular layer, in that the separation of keratohyalin is for the most part arrested, as it always is in abnormal moisture or abnormal compression of the epithelium. Often the granulation ceases altogether, often the granules are only very, very fine. In many cases where at the first glance they appear to be absent, one finds, immediately around the nucleus, a collection of the finest possible keratohyalin granules. But we must utter the warning that this disappearance of granules is not to be put forward as something inherent to every specimen, or indeed to every section. Nothing is more changeable in eczema than the amount of moisture in the upper epithelial layers. One can often enough find preparations which on every section show the same condition in the transitional epithelium. But in the majority of preparations the amount of keratohyalin varies from papilla to papilla. And this very punctiform and sudden change is really characteristic of eczema; in such a small space and so frequently, it is not present in any other disease.

In this circumstance lies also the explanation of the fact, that not only, on many places, is the granular layer well preserved, but that it may attain even a greater thickness than normal. This always takes place where the moist transitional layers are elevated, become cornified and replaced by younger after-growth; encapsuled. For, abnormally moist horny layer is naturally less brittle and therefore more coherent than normal; it does not, like that, scale insensibly, that is, in single horny cells, and small collections of them, but sensibly, in larger lamellæ, small scales. The greater coherence of the abnormally moist horny layer, transformed into a scale, but not yet thrown off, induces a greater delay in the process of cornification in the immediately following layers; in other words, a stagnation of granular cells, a broadening of the granular layer. Since the granular cells are no longer capable of division, every widening of the granular layer indicates merely *slowing of the process of cornification.* The departures from normal cornification which are shown in the widening of the granular layer and the simple delay of cornification, are therefore by no means completely contradictory and mutually exclusive extremes, but they may appear alongside and follow one another in the smallest space and with the greatest rapidity, and may indeed appear periodically on one and the same place. On the period of the greatest moisture, without keratohyalin, there follows immediately, a somewhat drier one with free separation of keratohyalin; we find scales totally deficient in keratohyalin, lying upon a broad granular zone.

What the absence of keratohyalin is to the granular layer, that is to the adjacent basal horny layer, a complex of three symptoms. We find here (1) *widening of the basal horny layer;* (2) *an abnormally small amount of fat in it;* and (3) *an abnormally good preservation of its nuclei.* The first two symptoms are best studied on osmium preparations. Then it strikes one at once that, instead of a black basal streak, the undermost horny cells remain light, and instead of having run together to a homogeneous band, show very clearly the outlines of the cells. Normally, in osmium preparations, the undermost layer of horny cells remain light; this is still moist, therefore free from fat and not blackened. But now, wherever in alcohol preparations, properly stained, disappearance of the keratohyalin and retention of the nuclei in the process of cornification are evident, there is seen, on the osmium pre-preparations, instead of a layer of cells, a whole series of super-imposed unblackened layers. The greasiness, that is, the dryness of the horny layer, first begins here, higher up, sometimes first at the outermost layer. The retention of the nuclei in the horny cells at this place is shown in every properly-stained alcohol preparation. It is not a fine nuclear granulation such as usually persists, but the complete, though shrunken and "rod-like" flattened nucleus. Its actual form is not rod-like, but round and flat, biscuit-shaped, so that it appears as a rod when cut in any direction; nor is the form of the horny cells of the scale spindle, but lentil-shaped.

But the widening of the basal horny layer extends still further. Under certain circumstances the whole horny layer has the same character, namely, when the altered œdematous areas of horny layer have freed themselves from the horny layer around them, and have developed into a uniform scale. Then there no more takes place the transformation (into middle and terminal layers) which the surface tension usually induces on the basal horny layer, and there is no reason why the abnormal basal horny cells should not be piled one upon another (into a scale) so long as they are formed. The single change which takes place in such a scale is a drying of the outermost cells, by which they become still smaller without suffering any change in their interior.

Parakeratosis consists then only in *an abnormally simple cornification*, that is, in the absence of the many intermediate stages (separation of keratohyalin, breaking up of the nucleus, drying-up of the internal protoplasm), which accompany normal cornification. The cell wall becomes cornified or hardened as usual, but the cell contents remain moister and better preserved. Therefore the developed horny cell rather resembles an older mucous epithelial cell, and, like it, is deficient in the natural protection which the absorption of fat, following on the

loss of water, provides. It is a striking confirmation of this view that the cells of such a parakeratotic horny layer (scales) can scarcely be distinguished from the cells of a simply dried-up prickle layer. It is well known that on the corpse where the horny layer is absent, the skin dries up. Now where in eczemas on the corpse the normal fatty horny layer is here and there replaced by a moist parakeratotic one, the prickle layer under it dries up from want of retained fluid, and the whole epidermis forms a dry pellicle. At such places one cannot distinguish scales and prickle layer from one another. Both show the same spindle-formed cells and rod-shaped nuclei, and take the stain common to dry structures. A scale is, therefore, only a hardened, improperly cornified prickle layer. Proper cornification is hindered by the abnormal saturation, the parenchymatous œdema of the epithelial cells.

2. *Acanthosis.*

Serous saturation of the whole epidermis can only exist for a short time without inducing further changes. Every long-standing eczema leads to **epithelial growth**. Clinically this is manifest in the papular elevations of the eczematous parts, and is then quite beyond doubt. But even where a general papular elevation is absent, signs of epithelial proliferation are present, if the disease is persistent. But in such cases it is compensated by the desquamation of the epithelium.

Mitoses, the visible sign of epithelial proliferation, are distributed in greater number at the connective tissue margin, most richly in relation to the papular elevation, but a few also in a pretty broad zone round about. But they are found not only here, but also well towards the middle of the epithelial ridges, and outwards near the horny layer ; they are therefore in abnormal positions. I have counted them in several preparations, and find that a third to a quarter of all mitoses are found in a central zone of the prickle layer far from the connective tissue, while two-thirds to three-quarters occupy their ordinary site in the germinal layer of the normal prickle layer, that is in the undermost two epithelial rows. The increased saturation of the whole epithelium, and the consequently delayed cornification, possibly enables the epithelial cells to retain their power of proliferation longer than normal. But a few mitoses are found so near the horny margin, that we must also consider the possibility that the infectious germ directly induces mitosis, as we know cantharadine does. Be it a primary action of the eczematous poison or a secondary result of the serous exudation, we always find epithelial growth as an accompaniment of every long-standing eczema. This cannot persist without a marked action on the form of the papillary body, which requires all

the more consideration, since for a long time, especially in the psoriatic form of eczema, it has been considered as evidence of independent proliferation of the latter. Chronic eczema has as little to do with independent growth of the papillæ as has psoriasis. Auspitz did good service in pointing out the power of the growing epithelium in deforming the papillary body, at a time when all more exact criteria of cell proliferation were still undiscovered. Even now one must, even without knowing the seat of the mitosis, solely on the ground of the deformity of the ridge system on the one hand, and of the papillæ on the other, come to the same conclusion. But the recognition of mitoses and their significance makes this fundamental histological question, which comes up in the consideration of so many dermatoses, much simpler. In the stage of the simple parenchymatous swelling of the epithelium, not only are the ridges broadened, rounded, and often at the same time elongated, but the papillæ lying between them are more or less swollen, especially widened at their apices, and here and there—corresponding to the ridges around them—moderately elongated. But no papilla is added, new formed, and none show a collection of young cells as an indication of an active lateral or terminal sprouting. If acanthosis is added to a long-standing eczema, the epithelial masses make themselves a place, partly by the ridges going deeper and flattening the horizontal plate of the papillary body, and partly by making the papillæ smaller and narrower. Both forms of deformity have the same result, viz., the papillary body is everywhere thinned and passively flattened out, in order to accommodate the increasing system of epithelial ridges, and to cover it as before. It always forms a thinned plate, seated on the cutis, with the same number of elongated and diminished papillæ. This passive extension may, without further disturbance, assume all the greater dimensions, the greater the papillary swelling at the commencement, and the more cellular infiltration occurs in course of the process. Indeed the latter may become so marked that passive elongation of the papillæ takes place without their diminution, it being over-compensated by cellular infiltration. But even in these cases we find no indication that the papillæ actively attack the epithelium and produce daughter papillæ. On the contrary, where we see fresh irregularities added to the simple primary deformity of the papillary body—which I have already characterised as a general thinning with extension of the surface—these are always **secondary furrowings** of pre-existing papillæ by irregularly-growing epithelium. At such places we invariably find mitoses in the advancing epithelium, and never in the adjacent connective tissue, such as the papilla, which indents the hair germ, shows, and as we are entitled to demand here. The "papillary growth" in eczema (and in psoriasis) is therefore false;

an enlargement of the pre-existing papillæ, there is: first, primary, from simple œdematous swelling, then secondary, from cellular infiltration. But usually the elongation of the papilla is accompanied by a proportional thinning. Every complicated formation of the papillary body is to be attributed to the accompanying epithelial growth. But with this the passive deformities of the papillary body are not exhausted; the papillæ may become shorter and completely disappear, withdrawing themselves from the advancing epithelium, and disappearing in the horizontal plate of the papillary body. There are certain forms of eczema which present this type of the papillary body, and since this form of deformity, and its relation to the others, comes into consideration not only in eczema, but also in many dermatoses, we must give a short *general* explanation of it.

It consists in the remarkably different appearances due to the epithelial growth, which partly repeats, with variations, the ridge form of the normal epidermis, but sometimes, instead of this, shows the prickle layer run together to a simple plate. If, to simplify matters, we completely ignore any independent increase of volume in the papillary body, then all these appearances can only be attributed to active epithelial growth. But if all these different deformities are to be explained by this uniform force, that is only possible with a *difference* of *resistance* in the deformed mass. It is clear that there must exist some point where this resistance varies, and that is the papilla, especially the apex of the papilla, still more particularly the *loop of blood capillary in the papilla.* In this limited area the peripheral blood pressure, which in the skin is only weakened by the muscles of the arterial wall, predominates, and it is evident that the epithelium, in its downward growth, meets here the greatest resistance. We cannot consequently regard the resistance of the cutis as equal. Wherever papillæ are formed we have always to do with two independent resistances, a *general cutis resistance* (R.C.), which comes into play only in the spaces between the papillæ, and a *papillary resistance* (R.P.), which is added at the seat of the papillæ. Evidently the definite form of the papillary body depends chiefly on the relations of these two factors, R.P., R.C., that is, it depends on whether the papillary resistance comes into play independently of the general cutis resistance, or not. In addition to these two resistances, the general and regular *resistance of the horny layer* (R.H.), is naturally also of great importance. Its existence is first made possible and necessary by the boring of the prickle layer into the cutis.

Now if we indicate the inter-papillary part of the prickle layer with In, the supra-papillary with Su, we have the following simple proportions between these two important factors. The inter-papillary

part of the prickle layer is increased by the epithelial growth, in proportion as the papillary resistance predominates over the general cutis resistance, and the greater the resistance of the horny layer is; naturally, also, it increases proportionately to the epithelial growth (Ep.) itself.

Consequently: *

$$\text{In} = \frac{\text{R.P. R.H.}}{\text{R.C.}}, \text{ Ep.}$$

The supra-papillary prickle layer extends the more, the less is the papillary resistance as opposed to the general resistance of the cutis, and the less the resistance of the horny layer; its growth is also proportional to the epithelial growth.

$$\text{Su} = \frac{\text{R.C.}}{\text{R.P. R.H.}}, \text{ Ep.}$$

As one sees the same factor: $\frac{\text{R.P. R.H.}}{\text{R.C.}}$ figures in both equations, in the one as numerator, in the other as denominator of a fraction, to be multiplied by the whole epithelial additions, that is, it occupies opposite relations in restricting the space of both parts of the prickle layer, or to put it plainly, the more voluminous the supra-papillary layer, the smaller is the intra-papillary. In a few cases, however, it is evident from the formula, that the supra-papillary layer becomes greater, that the prickle layer takes on more the form of a simple plate, the less is the papillary resistance or the resistance of the horny layer. Now the latter is in eczema (and in psoriasis) usually by no means minimal. For in the dry forms (and in psoriasis) even after the scales fall off, the uncornified epithelium is still covered with a particularly coherent basal horny layer; a complete falling off of the horny layer in the moist forms is always accompanied with such a mechanical rarefaction of the supra-papillary, spongy prickle layer, that one cannot well speak of a distinct increase in its volume. Certainly one most frequently finds in the chronic moist forms a visibly swollen, supra-papillary prickle layer. The factor R.H. never completely disappears in eczema, in spite of the superficial softening, because the *connections* of the epithelial cells are not loosened.

But if the simple plate form is visible in eczema, in spite of the retained horny layer, it can only depend on a disappearance of the other factor, the papillary resistance (R.P.). These are the forms which have a great resemblance to the purigo of Hebra, since the horny

* I know, of course, that for a complete formula other factors would need to be taken into account, especially the independent increase in the papillæ, as by œdema. Then the thing would be complete. But for our purpose what is mentioned suffices.

layer is much thickened, and the skin becomes poor in fat and very pruriginous. In these cases the skin—usually from birth—is especially poor in blood, and the tone of the cutaneous arteries is especially powerful and easily irritated (Urticaria). While, on the one hand, anæmia of the skin favours the excessive cornification of the epithelium, it diminishes the blood pressure in the papillary body, and with it the papillary resistance. Under such circumstances the papillæ, when epithelial growth sets in, retract considerably or completely from the ridge system, and the prickle layer assumes the form of a simple plate with very few, thin, often thread-like papillæ.

But this formation of the epithelium is the exception in eczema. As a rule the papillary and horny layer resistances are great, and therefore the inter-papillary prickle layer is well developed, while the supra-papillary is restricted to a few layers of cells. The papulo-squamous psoriatiform eczema and psoriasis itself form the extremes in this direction. Here the papillary and horny layer resistances are maximal, and consequently the supra-papillary prickle layer is minimal. This fact has an important clinical significance. There is a well-known tendency to regard the *bleeding* of the psoriasis papule, after scratching off the scales, as pathognomonic. It naturally depends on the excessive thinness of the supra-papillary layer, and further depends on the fact that the scales are still young, and pass gradually from the transitional layer without any sharp margin, and therefore the few prickle cells which separate the papilla from the scales are readily removed with them. Further, in the typical psoriasis papule, when it lasts long, distinct dilatation of the papillary vessels is present, so that these often occupy the summit of the papillæ. But, on the other hand, we find psoriasis papules in which all these favouring circumstances are not combined, and which, therefore, do not bleed when the scales are scratched off, and plenty of dry eczema papules in which the phenomenon of bleeding may be induced, since in them the firmness of the horny covering and the marked papillary resistance have reduced the supra-papillary layer to a minimum.

The epithelial proliferation always extends, in old eczemas, to the prickle layer of the hair follicles, but usually only to their upper part, and leads only to a general thickening, or not even to that, but there is no tendency to epithelial budding.

3. *Spongy Transformation of the Epithelium and Vesicle Formation.*

The commencement of this pathological change, which distinguishes all the moist forms of eczema, is seen in a general dilatation of the lymph spaces of the prickle layer, thus—in contrast to simple para-

keratosis—in an *interstitial* œdema of the epidermis. It is characteristic of this cellular œdema that its amount increases from within outwards, from the connective tissue margin towards the horny layer. The inter-cellular bridges are everywhere retained, but the inter-cellular spaces are so broad, that, with a suitable stain for demonstrating the margins of the epithelial cells (*e.g.*, water blue), they may be seen, even with the low power, as a wide net of canals, especially in the upper part of the prickle layer. Then some of the inter-cellular bridges give way, the epithelial cells, clad with short prickles, withdraw further from each other, some cylindrical ducts are converted into sausage-like, blown out, knobbed, or even rosette-like spaces, while others widen into larger, more uniform, prismatic or sack-shaped inter-cellular cavities. It is remarkable that no corresponding amount of wandering cells accompanies the excessive stream of fluid which converts the upper prickle layer into a coarse-pored, spongy tissue. In this earlier stage of the spongy development of the epithelium there are strikingly few leucocytes in the epithelium, hardly more than normal.

The character of the exudation in eczema is then, at the commencement, purely serous, only later does it become sero-fibrinous. In the inter-cellular network of cavities, there are precipitated, fine, granular coagula which, later, completely fill the cavity with granular coagulated masses. Now and again these are, from the commencement, firmer and more homogeneous, and give, although only faintly, Weigert's fibrin reaction. But these true fibrinous thrombi only exceptionally fill the epithelial spaces in the prickle layer; much more frequently—one may indeed say pretty regularly—the spaces of the already cornified epithelium, that is, the spaces in the crust. But these also hardly ever give, with Weigert's stain, a perfectly uniform reaction; there are varying chambered and storied coagulated masses of different structure and different reaction to Weigert's method. Many parts of the crust contain, then, a perfectly transparent, coagulated substance, which takes up neither the stain nor the contrast stain (picro-cochineal).

The extension of the spongy transformation of the prickle layer is very irregular. At the commencement we find it in points about the size of the breadth of a papilla, and, at first, always directly under the ordinary cornified or parakeratotic transitional layer; there are often several in one section. They may retain this normal size, and, cornified, reach the scale, and then, reaching over the surface as small knobs, form miniature, dense fibrinous crusts which are gradually thrown off. Or they extend concentrically from their point of origin outwards into the prickle layer. So also, when interstitial œdema is added to parenchymatous, the spaces dilate, and run together to larger inter-cellular spaces, while the previously swollen epithelial cells are partly compressed

into thin, cord-like rafters. After the holes of this spongy epithelium are partly filled at the upper margin with coagulated masses, the whole spongy area is elevated by the growing epithelium, dries up and becomes a fibrinous crust. These larger, and only slowly completely exfoliated crusts, now and again, even when they are cornified, soak up lymph like a sponge, and thus swell into very thick, loose structures; the yellow honey-comb crusts which are often wrongly considered distinctive of "impetigo." That these are only secondary is shown by the fully dilated, almost cubical spaces in the crusts, which are separated by fine perpendicular horny partitions, and filled with coagulated fluid; spaces which could not possibly have developed in the same form inside the prickle layer.

Thus is the epithelium affected in which the ordinary eczema vesicles are formed. It is a distinctly altered, softened, loosened epithelium, and the eczema vesicle* is only the final product of a slowly extending pathological process, to which from its physical character I venture to give the name of *spongy transformation of the epithelium.* How the eczema vesicles develope on this basis will be shown directly. But this is the place to draw attention to the fact, that this formation of vesicles, which I have seen repeated, without exception, in the same way in a very considerable number of (over forty) cases of moist eczema, by no means corresponds to the usual views on the subject, according to which the eczema vesicle, like that of Zoster and Variola, commences with a primary colliquation and degeneration of the epithelial cells. Nothing can be more incorrect than such a view. The elementary cavities in the prickle layer, which precede the formation of the eczema vesicle, develope only intercellularly, and are consequently *elementary vesicles of dilatation, and not elementary vesicles of colliquation.* The actual basis of the eczema vesicle is then a net-like, connected system of dilated canals in the most superficial part of the prickle layer, not, like most of the vesicles of colliquation, in the middle and under part of the prickle layer. Finally, the *surrounding epithelium,* during the formation of the eczema vesicle, remains for the most part absolutely normal.

Here, however, a slight exception must be noted. In long persistence of the spongy condition, and later, on the surface of larger vesicles, there are added to the small, intercellular, elementary cavities, certain others which are localised in the interior of the epithelial cells, at the seat of the perinuclear space, and arise from its simple dilatation. But these cells are a long way from being softened and degenerated in their substance. The outer mantle of the cells is indeed

* I ignore here the acute impetigo-like eczema vesicles, which develope from the sudden invasion of morococci into the prickle layer.

usually cornified, the inner cell substance, with its well-preserved nucleus, is compressed, and pressed to a side by the dilatation of the perinuclear space. It is then neither a reticular nor any other kind of degeneration, but simply the extension of the intercellular œdema into the lymphatic perinuclear space of the cell. It is the change first described by Leloir as the commencement of many vesicles under the name of "altération cavitaire," which begins in the perinuclear space, and does not depend on a primary degeneration of the protoplasm. I shall designate this transformation, which, in my view, only plays an unimportant, always secondary *rôle* in vesicle formation, as *cavernous transformation*—not degeneration. In eczema it is only now and again added to the previous spongy transformation of the prickle layer. Where it is present intra-cellular thrombi may naturally also be found.

But the sporadic presence of intra-cellular changes in a few preparations does not alter the fact, that the epithelial œdema of the prickle layer in eczema is mainly interstitial. There is entirely absent in the process any poisonous action which leads in any characteristic way to the degeneration and liquefaction of the protoplasm of the prickle cells. Indeed, in spite of the continuous soaking with fluid, the cornification of the epithelium is never absent. That this changes its type, we have already seen, but it is quite evident that cornification regularly occurs in eczema, that the serous cavities and fibrinous clumps lying in the epithelial spaces are always embraced by cornified epithelium, and are therefore heaped up in the form of crusts. There is no more instructive study than the histology of eczema for those investigators of the normal anatomy of the skin, who persist in assuming a necessary connection between the separation of keratohyalin and cornification. They may there find in every section that cornification proceeds even in moist, nucleated epithelial cells which have never separated keratohyalin, and that very firm scales and crusts are formed from horny cells, whose horny covering even resists peptic digestion.

Although the spongy prickle layer may contain many small elementary cavities, with or without coagula, it does not yet present any proper, *i.e.* macroscopically visible vesicle. But vesicles develope very readily on this basis, in two forms, and probably from two different causes. The one, according to my preparations, more common form of vesicle is nothing but a local excess of the spongy transformation of the prickle layer. One finds, on looking over many sections of eczematous papules, which macroscopically showed no vesicle on the under side of the crust, scale or simply parakeratotic horny layer, here and there globular cavities, which at their bases and sides pass into

the spongy epithelium without any definite margin. And one finds further the same appearances in sections of eczematous skin with visible vesicles, which show all the transitions which could be desired, from the small up to the large. These only differ, in that the larger induce a backward pressure on the spongy epithelium from which they have arisen by greater pressure of serum, and, therefore, are more sharply marked off from it. The position of the two is the same; they are always most numerous immediately under the horny layer, directly in contact with it, and extend outward in different degrees in the prickle layer. Their contents also are the same, namely, purely serous or fibrinous. These may partly or completely coagulate, and, like all large thrombi, in coagulating do not retract from the wall concentrically but in festooned segments, which correspond to a drop of serum expressed at the periphery. These thrombi then project into the vesicle as firm, globular, fibrinous processes, from the under side of the scale, and when the scale is removed, one sees on the surface a corresponding number of grooves in the epithelium.

While this form of vesicle is the direct consequence and only the extreme development of the spongy metamorphosis, the second form of vesicle is something quite new. Here we have no gradual transition, but a sudden abrupt change. Certainly it developes on the basis of the spongy transformation, but it is not a simple increased collection of serum which dilates the uppermost spaces into vesicles, *but a local saturation with leucocytes.* The sharp limitation and the considerable size correspond to the clinically rapid appearance of this vesicle, in virtue of which it usually compresses the whole surrounding prickle layer. The leucocytes almost completely fill these relatively large vesicles, so that there is only room for a small quantity of serum and granular coagulated exudation. This patchy penetration of the leucocytes at this *locus minoris resistentiæ* is further confirmed by the circumstance, that the surrounding prickle layer, in spite of the dilated lymph spaces, is usually comparatively free from wandering cells. It gives the impression as if all the leucocytes in the neighbourhood had run together at a sudden alarm, and, stopped at the horny layer, had made themselves a place, and thus, as in true impetigo, formed the sub-corneal vesicle.

Did we not already know from the whole history of eczema that the inflammatory irritant usually induced none, or a very, very slight chemotactic action on leucocytes, the true eczema vesicles, almost completely free from leucocytes, just described as the last stage of spongy transformation, would indicate that a local leucocytosis was not one of the necessary attributes of eczema. We are then directed by histology to look, in the second form of vesicles, for causes—outside the eczema—other than those of the first form.

Clinical experience confirms this view, for the vesicles which appear sporadically and periodically in the course of a chronic eczema, on already eczematous skin, are usually clear, and remain so till they form crusts, while those vesicles which by their sudden multiple appearance clinically justify the view that some secondary injurious irritant of general nature, *e.g.* an unsuitable drug, mechanical rubbing, a bath or the like, has induced them, usually appear yellow, opaque, and impetiginous. Hardly anywhere is the suspicion of a secondary action so justified as in chronic eczema, where the epithelium is permanently loose, which, on the one hand, facilitates the action of all external irritants and the absorption of all diffusible poisons, and on the other, greatly favours the saturation of these ways of entrance with exudation.

Now, what induces in individual cases the chemotaxis which leads to the development of leucocytic vesicles is, to our present purpose, irrelevant. The possibility that it may be organised poisons, especially pyococci, remains for future histological investigation, and is a very important question. We have only to place this form of impetigo-like eczema vesicle in its proper place, and to distinguish it, on the one hand, from the non-leucocytic vesicles already described, and on the other from the primary vesicles specially considered at the commencement of the chapter.

The two forms of vesicles just described as secondary to the spongy transformation, have in common that they appear *secondarily* on an *already eczematous epidermis*, that they are consequently *covered* with *crusts*, rarely with scales or parakeratotic horny layer, that they definitely show their *origin* from the *spongy epithelium* by their partial transition into it at their base or sides, and that their contents are uniform—namely, pure *exudation*. They only differ from each other in that the one has *pure serous* or *sero-fibrinous* contents, and is *small*, while the other is *packed with leucocytes* and usually *large*.

Opposed to them are the vesicles described at the commencement, which appear *primarily* on *otherwise healthy epidermis*, are *not covered by crusts* or scales, show *no transition* into *spongy epithelium*, and whose *contents* are a mixture of serum, leucocytes and uncornified epithelium, consequently *not a pure exudation*.

I have already shown that this variety of vesicle developes by the sudden entrance of morococci under the horny layer and into the prickle layer, either spontaneously or by inoculation. They alone represent *true acute eczema*, and their connection with the general chronic disease is shown by the identity of the infective agent.

From this we may conclude that the two other varieties which develope in the chronic disease do not exactly resemble the first in

their etiological relations, and, as a fact, morococci are very rarely found in them. They are never found in the pure serous and pure fibrinous small vesicles, any more than in the elementary cavities in the spongy prickle layer. From this it follows that the vesicles never develope from the immigration of the leucocytes from above, but only by the powerful attraction of a serous exudation from below. Consequently we find the morococci regularly, only in the overlying crust or scale, and usually, near the older mulberry-like groups, are fresh scattered younger groups, to which the new exudation is to be attributed. In the secondary leucocytic vesicles, also, I never for a long time found morococci, but recently I have been able to find them, though certainly in small quantities. But this exception does not upset the statement, that no penetration of morococci takes place in the genesis of these vesicles. The attraction which morococci and leucocytes have for one another explains how, in long-standing cases, single morococci may be taken up from the crust by wandering cells from the vesicle, but we never find here a saturation of the vesicle with morococci, or many of them being taken up by the leucocytes, as in the primary eczema vesicle. Here, also, the cause of the vesicle is to be looked for solely in the increased attraction of exudation from beneath; in this case a leucocytic exudation.

There still remains the question whether this exudation is induced by the same infection as usually induces the serous, or whether a more prolonged action of larger masses of cocci gradually leads to a local leucocytosis. And in support of this one might mention, that in the primary vesicle the sudden penetration of the morococci, previously growing in the horny layer, induces, in addition to the serous exudation, a considerable amount of leucocytosis. But, on the one hand, there is found in this vesicle no considerable number of cocci, and on the other, all histological and clinical evidence shows that these vesicles arise acutely and in large numbers at once. To me it appears only possible to regard, as indicated by the clinical history, causes lying outside the eczema as responsible for the sudden and abundant leucocytosis in this vesicle. No doubt, in certain cases, the addition of a staphylogenic suppuration comes into consideration. But I have not yet been able to recognise staphylococci in the cover of the vesicle.

4. *Changes in the Connective Tissue.*

Part of this—namely, the deformation of the papillary body—we have already described, when considering the epithelial growth. We saw that it usually led to the development of very long and thin papillæ, which were neither increased nor diminished in number as

compared with the normal, that comparatively rarely the papillæ disappeared by the flattening of the papillary body, and that in very active acanthosis now and again new smaller papillæ, which were seated on the older as daughter papillæ, were excavated. And further, in the course of chronic eczema, that there often developed an œdema of the papillæ, especially of their upper ends, giving them the appearance of clubs. In all these changes of form there were no signs of active proliferation.

But such are found in a growth of the connective tissue cells, accompanying every eczema, chiefly developed around the sub-papillary vascular net, and therefore not inside the papillæ. While the sub-papillary vascular net, in long-standing eczemas, is always surrounded by a broad zone of proliferated perithelium, the new-formed cells diminish along the papillary body and cease, usually below its summit. The horizontal plate of the papillary body is usually, even at a distance from the blood vessels, closely permeated by cells, the connective tissue of the papillæ only sparingly so.

In the cases with moderate cellular infiltration, the infiltration along the vessels diminishes rapidly from the sub-papillary vessels downwards, while the parts lying between remain quite free. The greater the infiltration the more are the inter-spaces filled with young connective tissue cells, so that finally the whole cutis, and especially the surroundings of the coil glands, are pretty regularly infiltrated. However pronounced the thickening, the cellular infiltration never goes beyond the border of the panniculus. In certain forms the panniculus, in the course of the affection, increases at the expense of the cutis (alopecia seborrhoica), in other cases it gradually disappears (pruriginous eczema).

As to the nature of the cellular infiltration, it is at the first glance little characteristic, being chiefly distinguished by negative signs. There is, firstly, *no disappearance of the collagenous tissue.* Thus the young cells often lie in rows between the collagenous bundles, and the infiltration forms a sort of net in the cutis. This persistence of the collagen causes the firmness of the infiltrated parts in eczema.

Then the elastic tissue does not disappear, at least over the greater part of the eczematous skin. Even into the papillæ, fine fibrils ascend and form a sub-epithelial net as usual. Only in very dense infiltration around the vessels do the elastic fibres there become thinned and finally disappear. Finally, the *absence of leucocytic emigration* is most striking. In order to be able to settle this point, one must of course examine pieces of skin, which present only the ordinary condition of chronic eczema, and are not, or have not recently been in a condition of artificially-increased inflammation. Then there is hardly any

emigration of leucocytes. One can here decide this, more definitely than usual, since a persistent although slight emigration would necessarily affect the deep growing epithelium with its wide lymph spaces; indeed the leucocytes would actually crowd it. In such uncomplicated cases we find very few wandering cells in the epithelium, hardly more than normal, which, considering the amount of fluid in the eczematous skin, signifies much. Only during periodical increased inflammation do we find collections of leucocytes in the capillaries, and a regular infiltration of the upper part of the cutis with wandering cells, all making for the epithelium, so that this also is infiltrated with leucocytes; and finally, leucocytic vesicles. These are the cases which, in describing the last form of vesicle, I have indicated as probably outside the category of uncomplicated eczemas. These cases are relatively rare, and differ in the presence of leucocytes so much from the ordinary eczemas, that we shall do well not to regard them off-hand as typical.

What then are the positive characters of the eczematous infiltrations? They consist mostly of *small multiform connective tissue cells, poor in protoplasm, lying closely together, and having a well-, but not very deeply-stained nucleus.* With protoplasmic staining they present no marked granulation. Their initial form is best studied, not in the neighbourhood of the vessels, where they lie too closely and are usually cubical, but in the slighter infiltration of the cutis lying between. Here they appear mostly as spindle cells, which have the peculiarity that they remain strikingly small, that the processes by which they are connected are short, and they consequently lie close together. Compared to these small, faintly-stained, but otherwise ordinary connective tissue cell constituents of the infiltration, the number of plasma and mast cells is distinctly small. The plasma cells are only present in long persistent dense infiltrations, and then they are only scattered in small groups at the seat of the densest infiltration, especially around the larger vessels and the coil glands. The mast cells also are not especially numerous in eczema, which is the more striking, as there is a vigorous epithelial growth which is usually accompanied by increase in the mast cells. But in a few cases of old chronic eczema I have found them present in considerable numbers.

Further, the small number of mitoses inside the infiltration is remarkable. I have several times succeeded in finding them, especially in the vascular endo- and peri-thelium, but in very small proportion compared to the amount of readily recognisable epithelial mitoses. But one must not forget, that the infiltration in the cutis is developed very slowly, and although, in cases of marked infiltration, the number of dermal cells is striking compared to that of the epithelia, these latter are, in eczema, constantly being renewed, and therefore the

frequency of mitoses is not so striking. Further, one may examine parts with marked epithelial growth, which have for a long time remained stationary, in which not a single epithelial mitosis is found in many sections. The moderate number of connective tissue mitoses is therefore, in eczema, no ground for assuming the amitotic origin of part of the cells of the infiltration.

Finally, characteristic of the eczematous cutis, the blood and lymph vessels are almost always dilated, and the cellular infiltration, in excessively infiltrated cases, is gradually and very regularly thinned off at the border next the healthy cutis, until it is finally limited, as in the slight cases, to the papillary body.

5. *Retrospect.*

Before we enter upon the consideration of certain important details and complications, it appears desirable, after this description of the three main histological symptoms of eczema, to take a survey of the combinations of these symptoms with each other, their developments, and their healing. From this consideration it will be evident that the commonest forms of eczema present a mixture of the three symptoms described above.

Parakeratosis is the most important symptom of eczema; it is never absent, even in the slightest forms; it is pathognomonic of eczema. Where it exists alone we have a condition of the skin known as *Pityriasis alba*, sometimes diffuse, sometimes circumscribed, *e.g.* on the head or face, which is *the first elementary form of eczema.* The scaly condition heals, a dry layer of cells, which separates keratohyalin and cornifies in the regular way, forming underneath the parakeratotic horny and transitional layer. The greater adhesion of the parakeratotic horny layer prevents the separation in insensible scales, and they consequently for a time remain adherent. When they fall off, the surface is smooth and even.

If *acanthosis* is added to parakeratosis, the affected area of skin appears as an elevation, from the size of a mustard seed up to that of a shilling, with a scaly surface. We have then the dry, small or large, papular eczema, the second elementary form of eczema. The healing is then less simple. The mere replacement of the scaly surface by a normally cornified one does not induce healing, and does not usually take place unless the epithelial growth has previously ceased. In addition to these, the deformity of the ridge system, and the secondary deformity of the papillary body, must have disappeared.

If the parakeratosis go on to moist eczema, there ensues *spongy transformation of the prickle layer*, and if the exudation is greater,

vesicle formation, and thus results the crusted form, with or without vesicles; the third elementary form of eczema. The healing of this form takes place in very different ways, according to the quantity and quality of the exudation. In general the contents of the vesicle take a more definite form, the further the encapsulation is advanced, and the smaller they are. But there are also large vesicles in the prickle layer which are enclosed by a very, very thin layer of cells, and nevertheless have completely coagulated contents. The necessary result is that these vesicles, in the process of encapsulation, and during their elevation, attain a compressed spherical form, and give origin to lenticular, globulary swollen, thick crusts, which, after their complete encapsulation by the regular horny layer, still lie in a depression of the epidermis. But if coagulation of the contents is delayed, the vesicles, as they rise and as they are encapsuled, acquire a more straight, stretched form; the rounded chambers become cubical, and the oblique walls perpendicular. These are the cases in which the crusts, during the process of encapsulation, still soak up new exudation, and consequently often reach an enormous thickness. The regular course of eczema, with its periodical appearances of congestion, is that the formation of vesicles is repeated time after time, on the same place, before healing ensues. Thus there is developed a sort of storied formation, in that, on the old, thick, coagulated crust, there is a fresh, loosely coagulated one, and on this often a fresh vesicle in the prickle layer.

The parallelism of the appearances of exudation with the bacteriological relations of the crusts and vesicles is very instructive, and to me almost proves their parasitic nature. The moist crusts, after coagulation, form an excellent medium for the morococci, which, as the crust dries, form larger and larger mulberry-formed collections. These we find constantly in the old, long undisturbed crusts, and, naturally, they are most clearly seen in the transparent contents of clear coagulated vesicles. As they further dry, the crusts split perpendicularly to the surface of the skin, and thus the morococci get the opportunity of growing from the warmth and moisture at the tear, until they reach the base of the crust. Now in the cases in which, under the encapsuled vesicles, new ones are formed, one finds almost regularly that the morococci on the base of the old—that is, the covering of the new—vesicle have taken on a new and vigorous growth. We will not go far wrong then in assuming, as we have above from other grounds, that these vesicles under the middle of old crusts are the results of the multiplication of the cocci in the latter, and the consequent attraction of a new flood of serum.

The healing of the simple combination of parakeratosis and vesicle formation is naturally simpler, when epithelial growth is not added to

them. In the former case simple encapsulation and separation is sufficient to restore the normal condition of the epidermis, in the latter case complete restitution is made more difficult, as in the simple papular eczema, for the deformed prickle layer and the papillary body must first be restored to the normal. In this lies the reason why in general the simple moist catarrhs heal so much more rapidly than the dry or dry papular.

In the following paragraphs I consider certain special eczematous conditions which have not been sufficiently referred to.

6. *Status spongioides—Eczema rubrum—Non-infectious recurrent eczema.*

We have become acquainted with the spongy transformation of the prickle layer in the moist forms of eczema as a somewhat transitory and at the same time sub-acute condition, which, at an acuter stage, shows vesicles, but which can heal by encapsulation. But there is also a chronic spongy condition, a loosening of the epithelium, whose recognition is practically of the very greatest importance.

Indeed it is not difficult to comprehend that this condition, at first brought about by particular chemotactic influences of an infectious nature, may continue to exist without their further action, and be prolonged by other less important factors. For we have not to do with a degeneration of the epithelium, which imperatively requires replacement through new formation, but at first, only with a predominance of the lymph spaces over the parenchyma. All the time, as I have shown, the cornification goes quietly on and acts to the "insensible" exudation as a sponge-like reservoir which we call a crust. If we simply continue to remove these crusts without otherwise acting on the eczema, we induce artificially the "spongy state" to which the name of *eczema rubrum* has long been applied. There is then visible a moist, loosened, red surface, swollen from the absence of the pressure of the horny layer, which, from the invisible pores of the dilated lymph spaces of the well-preserved epithelium, is constantly exuding serum.

The lymph tracks are here, once for all, dilated; they must constantly permit the escape of fresh serum, even without new chemotactic influences coming into play. It is at first not very apparent how such a condition can heal; at all events it has no tendency to it, and may exist for years without evident change; indeed it is well known that this spongy condition of the limbs is the so-called "sore leg" of old people. Epithelial cells have not the power, when they are drenched with lymph, to draw themselves together to dam up the

stream and so to restore the normal conditions. Therefore an Eczema rubrum never heals without scaling, that is, never without the young epithelium encapsuling the old spongy area and replacing it. One sees that for actual healing there must concur—a spontaneous (*e.g.* by medicaments) damming up of the escape of fluid, and the possibility of a new formation of young epithelium. In so far as the crusts, by their existence and their pressure, further the damming up of the lymph stream, they also tend to healing, and their artificial removal, on the other hand, to the permanence of the spongy condition.

But one sees at once that the absence of very simple and trivial factors is sufficient to delay definitely the healing of this condition. We can clinically distinguish three forms, the *pure serous*, the *purulent*, and the *cornified* (*chrysaloid*). The first form of Eczema rubrum depends simply on excessive loosening of the epithelium. So much serum is present, that the cornification of the superficial epithelium cannot keep pace with it. There is no formation of crusts, but at the most of loose fibrinous coagula, and these, as soon as they are formed, are washed away. To this form certain individuals are predisposed, and in them every eczema takes a very moist form; their epithelium must be specially vulnerable. As in bleeders bleeding goes on because the requisites for the healing of the wound in the vessel are absent, so in this case the eczemas continue to weep; the epidermis has simply become too leaky. The histological appearance is that of the simple spongy transformation in its highest degree.

The *second, purulent* form of Eczema rubrum is more frequent and more often attributable to local conditions. To it belong, among others, most old eczemas of the leg. Here it is not simply the excess of exudation which hinders healing; but partly a delayed growth of epithelium, partly some foreign, probably parasitic influences, which are still hidden from our knowledge. The histological appearance here is quite characteristic. The spongy transformation affects wide areas of the upper layers of the epithelium; all its lymph spaces are packed with leucocytes. Large vesicles are not developed simply because the resistance of a crust is absent; but one finds everywhere, under the surface, small, elementary vesicular dilatations which also are filled with leucocytes. The purulent transformation of the exudation naturally leads to a diminished tendency to coagulation, and perhaps also to a lesser proliferation of the epithelium. Both tend to delay definite healing. Whether a transient action of staphylococci causes the suppuration is still to be determined.

The *third form* of the spongy condition is perhaps the most important, because it is difficult to recognise clinically. Here we have no so-called Eczema rubrum; the surface appears to be normally cornified.

We see alongside spongy areas, which usually carry scales, crusts or a parakeratotic horny layer, others, which are covered with normal horny layer, indeed with a broad granular layer, and these at the first glance appear healed. We see, on the surface, remains of crusts, and have thus proof that here an eczematous process has been encapsuled and brought to a stand. And yet the prickle layer is not altogether normal but, although only slightly, spongy, that is, the lymph spaces towards the surface are wide. It is also possible that, in the encapsulation of spongy epithelium, the young epithelium is not exactly completely normal, but presents more roomy lymph tracks than a healthy prickle layer. However unimportant this histological condition may appear, I recognise in it the basis of an important clinical condition, namely, the *non-infectious recurrences of eczema*. Since, as we have just seen, the spongy transformation has in it the seeds of persistence, it is comprehensible that every increased exudation, which may have no connection with the actual cause of eczema, may, after a long time, and on apparently healed eczematous areas, produce fresh crusts and vesicles. The areas of the cornified or chrysalis-like spongy condition form a persistent *locus minoris resistentiæ* so long as it is not completely replaced by healthy epithelium, with normally narrow lymph spaces. Probably this condition is furthered by a too rapid cornification, without at the same time sufficient elevation of the part by epithelial proliferation.

The possibility of such a predominance of the spongy condition under a young horny covering explains the presence of certain—certainly rare—eczema vesicles, on whose covering we find neither the remains of crusts nor morococci, and in whose contents we also find no cocci. Such cases I have only, with approximate certainty, observed twice in seventy-three cases of eczema, of which forty-three were moist. I say approximately, for there is always the possibility that a central section, which might have contained the cocci, was overlooked. But in spite of the weight of evidence which lies in the constant discovery of cocci above (or in the primary also in) the vesicles, I would still regard it as possible, that in certain cases with persistent local recurrences, the cause is only to be sought in a chrysaloid, spongy condition of the prickle layer.

7. *Status hyperkeratodes—Eczema keratodes—Eczema rimosum.*

We meet an exactly opposite secondary phenomenon on the eczema of the palm of the hand and sole of the foot; an excessive collection of cornified epithelium. This appearance also is readily understood from the general histological relations of eczema, and especially those

of the affected regions. In them not only is the prickle layer always more thickly covered, but, necessarily associated with it, the cornification is particularly firm. Then we have the very perfect lubrication of this thick horny layer provided by the coil glands, for in spite of its thickness it must be able to follow the rapid movements of the hand. The horny layer is therefore elastic in the highest degree.

Of the main changes here, parakeratosis is the chief; epithelial growth is relatively not so marked, and vesicle formation is limited, like the spongy transformation, chiefly to the uppermost layer of the prickle layer. The intensity of the cornification leads to the heaping up of very thick, parakeratotic, hardened scales, which evince their firm connection by their extent (eczema keratodes), and these are not only thicker and therefore more difficult to move and fold, but also moister than the normal horny layer. Therefore they absorb less fatty coil gland secretion, cannot resist evaporation, and dry as far down as the deeper layers, which are moistened from beneath. Thus their elasticity is lost, and in place of the coarser lines of the skin, there are deep tears, appearing first in the scales. But as these pass directly into the spongy, swollen prickle layer, the tears often extend into the latter, are painful, and bleed readily (eczema rimosum). It is well enough known that an artificial saturation of the scales with grease at once betters the condition. The existence of eczema keratodes is therefore a proof that eczema is compatible with the presence of dense cornification and exerts its influence only on the contents of the horny cells.

We find in eczema, even outside the palm of the hand, now and again, a tendency to cracking of the horny layer, especially in long-standing eczemas of the extremities. In these cases it is due to the cracking of very thick crusts under the influence of great superficial drying. These tears, also, may directly extend into the spongy prickle layer in contact with the crusts. As these long-standing thick crusts contain the main groups of morococci, and these grow especially on the torn part of the crust exposed to the air, these tears in old crusts are usually the seat of the commencement of the new serous exudation into the underlying epidermis, and they therefore attain an important significance.

8. *Status pruriginosus, Eczema pruriginosum.*

We have still to describe another and even more important condition of excessive cornification in eczema, which, in addition to this symptom, presents a series of others still more striking, especially pallor, pigmentation of the skin, and very severe itching. This is not a pre-formed and regionally limited, but an acquired and general condi-

tion of the skin, which only affects certain eczematous individuals, and these mostly in early youth. Children so affected have a flabby dry skin, more pigmented than usual, scratch themselves constantly, frequently show urticarial eruptions, sleep badly, and give the impression of insufficiently-nourished subjects. The disease, from the parts usually affected in infancy (especially the head, neck, backs of hands, and genitals) extends more and more to the extensor surfaces of the extremities, without completely leaving its original seat. Especially on these places the horny layer becomes thicker every year. The coarser lines of the skin become deeper, and the skin can only be pinched up with difficulty, and in thick folds. It is more deeply pigmented, but is no more flabby, as it was in childhood, but, as it were, stretched round the bones, and is with difficulty movable, although the panniculus is very atrophic. Where actual moist eczematous spots are not present, the skin has an anæmic appearance. Scales, crusts, and vesicles are usually found on a few severely scratched places. From time to time the condition developes into a universal, moist, excessively pruriginous one, but profuse weeping is not developed. In the intervals of rest, where the thickening of the horny layer and the pigmentation alone persist, there appear small, itching, urticarial nodules, which either rapidly disappear or are scratched. Further, some cases show persistent spots of ordinary seborrhœic eczema, especially in the face, on the head, and in the flexures of the joints. The superficial glands are usually, although not severely, swollen. The general condition is better or worse in accordance with the acuter exacerbations.

As one sees, these cases present much resemblance to the prurigo of Hebra, and, in places where this is practically unknown (Hamburg, England, North America), they take its place, and are often enough regarded as true prurigo. The pruriginous stage of eczema differs from prurigo in that (1) this condition is not limited to the extensor surfaces, although these often present the pruriginous type, the flexor surfaces show rather the type of ordinary papular squamous eczemas; (2) these cases always present a previous history of ordinary eczema, and prominently show the transition into such (especially in the face); (3) the course of the disease is more varied, on periods of universal moist eczema, intervals follow with very slight pruritus, and indistinct papular and urticarial eruptions, while the simple prurigo presents a more even condition, which neither degenerates into severe exacerbations of the type of universal eczema, nor presents periods of apparently almost complete healing. (For the histological differences, see Prurigo.)

But the changes which, in course of time, take place in the skin, point to a basis common to both processes, and this I find in an *increased vascular tone of the affected individuals.*

Clinical proofs of this, lie—(1) in the anaemia of the skin; (2) in the tendency to urticarial eruptions; (3) in the vague but constant pruritus. Histologically, also, everything points to an increased vascular tone. The vessels are narrow, and the ordinary dilatation of the capillary system is absent. The blood pressure of the capillary vessels, diminished by the increased arterial tone, results in a diminished papillary resistance. Consequently the papillæ retract from the growing epithelium, and the excessive ridge system of the epidermis is transformed, in contrast to all other eczemas, into a more uniform plate, and the papillæ are diminished in number and in size. The diminished supply of blood and oxygen to the epithelium, on the other hand, favours cornification, and especially on the extensor surfaces of the extremities there developes, in course of time, thickening and extraordinary hardening of the horny layer. This, together with the flat form of the prickle layer, leads to the coarse lines on the pruriginous parts. It has much wider reaching results. For the general hyperkeratosis alone induces the unusual leathery hardness, the great tension, and the tightness of the skin on the extremities. Previously I believed that this was to be ascribed to a special development of the musculo-elastic system of the skin. But further microscopical examination showed that this, although not stunted, could not be regarded as hypertrophic. The hardness of the whole cutis at these places must consequently be ascribed to the special firmness, hardness, and diminished elasticity of the epidermis, especially of the horny layer. Naturally also the atrophy of the panniculus has a share in it, and this no doubt depends, on the one hand, on the diminished supply of oxygen to the skin, and the consequently lessened activity of the coil glands; on the other, on the increased pressure inside the skin, by which the fat-containing lymph is more rapidly conveyed away; possibly the general nervous condition of the patient, which is not favourable to putting on fat, also plays a rôle.

When urticarial phenomena are prominent, we find the lymph spaces of the cutis, especially around the vessels, dilated. They show an extensive but not excessive cellular infiltration of their sheaths and of the perithelium. Only at the time when severer eruptions are present, is the cellular infiltration more developed, although always less so than in other forms of eczema, in spite of the long duration of the condition.

The shortened and diminished papillary body is less infiltrated with cells. Most of the new connective tissue cells are found along the vessels, especially those of the papillary system. Plasma cells I have never found, but I have found mast cells regularly and sometimes in abundance. The prickle layer is in a state of parenchymatous swelling; the

horny layer is thickened and lies, where it is not parakeratotically changed, over the well-developed horny layer. Spongy transformation is only present on limited spots, is restricted to the immediate neighbourhood of the horny layer, and, like the vesicles which proceed from it, remains minimal. Parakeratosis and scaling, without marked papular epithelial thickening, vesicles or crusts on the one hand, urticarial phenomena, along with proportionately slight cellular infiltration, and erythema on the other, characterise the eczemas dependent on this basis.

9. *Status psoriasiformis.*

One has only to think of the opposite condition of vascular tone, an especially weak one, with all its consequences on the eczema which developes, and one has a type which comes very near the appearances of psoriasis, if it be not exactly one with it. The skin is well supplied

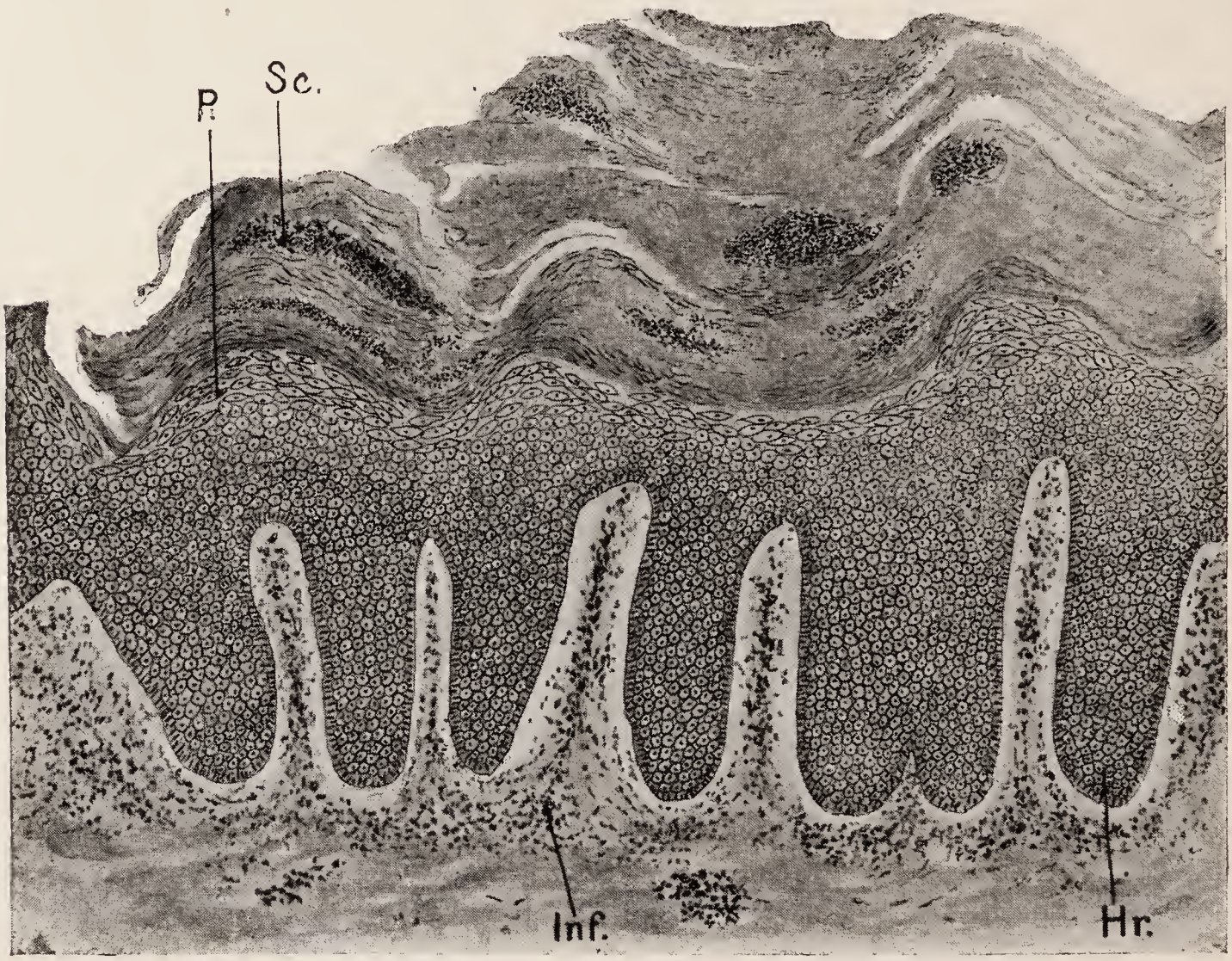

FIG. 6.—Eczema psoriatiforme of the elbow. Alcohol. Picro-carmin.

Inf. Cellular infiltration of the papillary body.
Hr. Enormous hypertrophy of the inter-papillary prickle layer.
P. Parakeratosis of the transitional layer.
Sc. The horny layer transformed into a scale, with scattered enclosed leucocytes.

with blood, readily tends to parakeratotic hyperæmia, but, on the contrary, not to urticarial phenomena, while it certainly does not readily itch. The abundant supply of oxygen induces a lesser firmness and

thickness of the horny layer, an easily-injured epidermis, but also a profuse growth of epithelium. The panniculus is well developed, the skin is easily pinched up, and feels soft and delicate. The colour is light; there is no pigmentation.

At the eczematous spots, the epithelial growth predominates over the hyperkeratosis, and, on account of the strong papillary pressure, there is everywhere marked development of the ridge system, while the supra-papillary prickle layer remains relatively thin. The profuse epithelial growth, in combination with the yielding horny layer, induces an arrest of the œdema at the parenchymatous stage. There is developed parakeratosis and profuse scaling; more rarely spongy transformation, vesicles, and crusts. The scales are mostly dry, crumbly or greasy, are readily heaped up, but may be easily removed, and punctiform bleeding sometimes ensues. Itching is less than in other forms of eczema.

One sees that these nummular, or—if they spontaneously heal in the centre—annular forms of dry eczema, approach psoriasis histologically as closely as they do clinically. To me it is not possible to draw a dividing line. The type psoriasis only presents the extreme of this condition.

10. *Status herpetoides.*

Now and again the moist, crusted, vesicular eczema is accompanied by a localised severe œdema of the skin. It is shown in herpetic groups, the size of a sixpence to half-a-crown, of closely placed vesicles, which appear in patches on the backs of the hands and fore-arms, and are also—and often symmetrically—seen on all the extremities. On these spots the skin tends, on the least irritation, to swell up, so that it is elevated several millimeters above the level of the surroundings, while it is much reddened, weeps profusely, and itches much.

Histologically we find that the swelling is by no means the result of an active epithelial growth or an excessive infiltration of the cutis, but is a simple œdema of the papillary body and the whole cutis. Crusts and vesicles are usually quite filled with leucocytes.

Inflammatory œdema, as an accompaniment of eczema, is by no means rare, but it is, in most cases, the result of secondary chemical or physical influences (unsuitable medicaments, the action of cold, too tight bandages, etc.). Even the so-called "acute eczema" of Hebra is in many cases only eczema * affected by secondary œdema, which, on the disappearance of the œdema, is again evident and follows its own course. But in the herpetoid eczema we have evidently to do with an inflammatory œdema, which is strictly limited to the seat of the eczematous eruption, and is induced by it. We must therefore, in study-

* In other cases it is simply an acute inflammatory toxic dermatitis.

ing the further appearances which belong to the question of eczema, also admit an influence of the vasomotors of the skin, though certainly only manifest in certain individuals, and not always in the same way.

11. *Status seborrhoicus. Seborrhœic eczema.*

Very frequently eczema is distinguished by a richness of fat in its products, and a yellowish colour of the rest of the skin, which is to be ascribed to fat. A great part of the seborrhœas described by the Vienna school as simply hyper-secretions, especially the so-called *Seborrhœa sicca*, are really eczema. For these diseases of the skin are accompanied by superficial inflammation of the cutis, parakeratosis and epithelial proliferation, sometimes pass into the well-known moist forms of eczema, and are likewise always accompanied by the morococci of eczema. The same is true of the Seborrhœa corporis of Duhring, the Lichen annulatus serpiginosus of E. Wilson, the "flannel rash" of the English, and probably also of *Pityriasis circinata et marginata of Vidal.* Therefore the definition of catarrh of the skin must be considerably widened, at the cost of that of the anomalies of glands, and I have done this by the introduction of Seborrhœic eczema, which includes the familiar as well as other forms, and has simplified the comprehension of a series of other affections, especially of Rosacea, not usually reckoned with eczema.

The addition of seborrhœa to eczema has a varied influence on the other histological characters. Parakeratosis is the least changed; its persistence, and the constant scaling of the epidermis which accompanies it, leads to the fact that the eruptions most resemble those of dry eczema and psoriasis. The interstitial œdema, which succeeds the parenchymatous, and goes on to vesicle formation, is distinctly diminished by the seborrhœa; most seborrhœic eczemas belong to the dry catarrhs. Certainly there are very frequently serous and fibrinous vesicles on the under side of the seborrhœic scales, and these are then converted into very fibrinous crusts. But on many areas of the skin, where the separation of fat is considerable, vesicular formation is limited to definite parts of the eruption, as on the sternum, to its border or to the mouths of the follicles, and there then develope composite elementary forms, synanthems of eczema. (See Typus circumcisus, Typus petaloides.) Equally comprehensible, as the limitation of excessive secretion by a greater richness of the tissue in fat, is the fact that, where exudation is in excess, the characters of seborrhœic eczema, both clinical and histological, disappear, and the appearance is again that of the non-seborrhœic. In profuse weeping eczemas, even in slightly weeping eczema rubrum, we can no longer recognise the original seborrhœic

origin, and can only assume it from dry, marginal seborrhœic parts or eruptions of that nature elsewhere, and that clinically as well as histologically.

Exactly opposite is the action of seborrhœa on the symptom of epithelial growth, which is hardly anywhere so pronounced, in eczema, as here. It may be that the formation of mitosis in the epithelium is directly favoured, or that the epithelial cells become more lasting, do not become old, and do not undergo cornification so soon; certainly

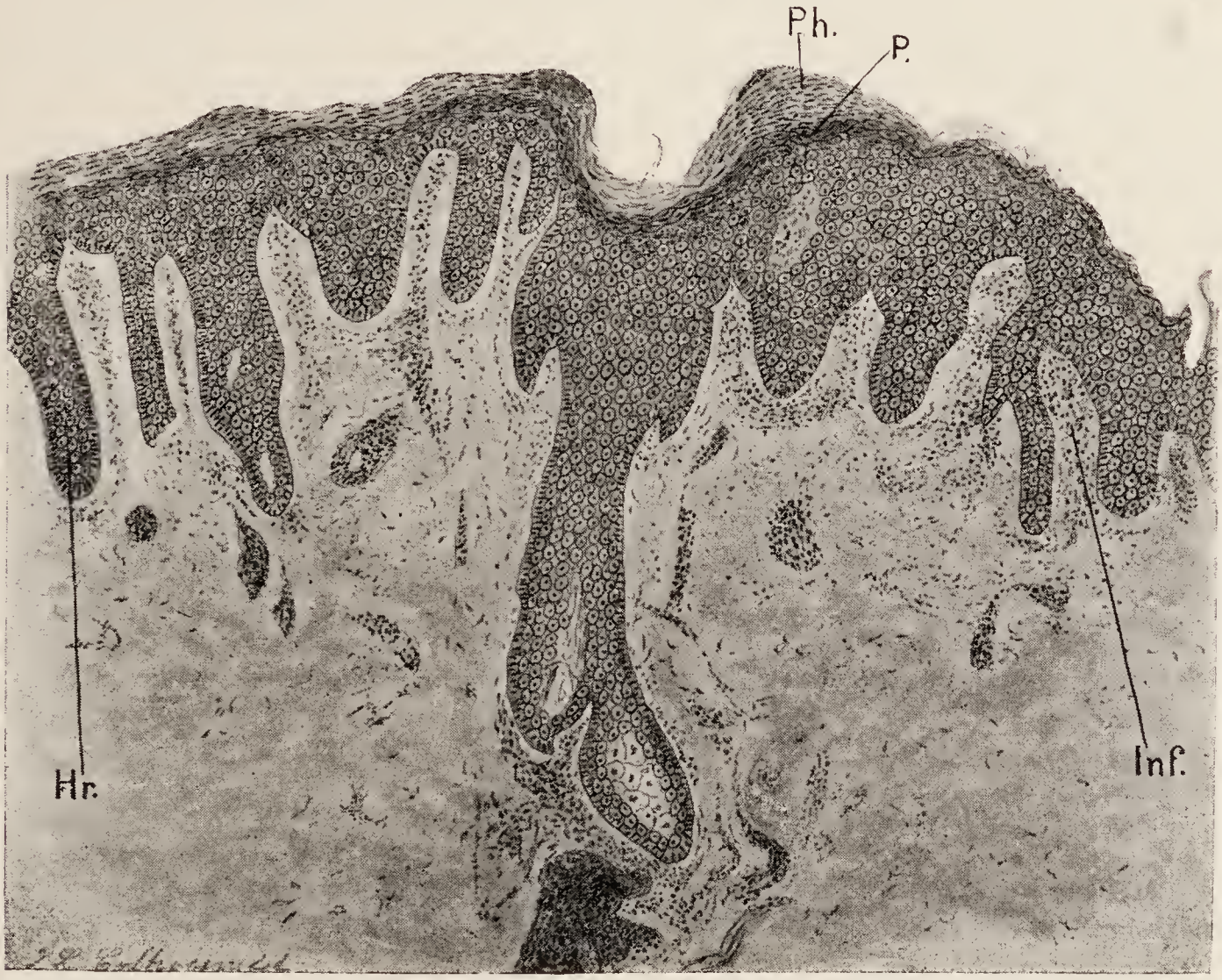

FIG. 7.—Eczema seborrhoicum sterni. Alcohol. Methyl-blue.

Inf. Cellular infiltration of the papillary body. *Hr.* Hypertrophic ridges of the prickle layer.
P. Parakeratosis of the transitional layer.
Ph. Parakeratotically altered horny layer, with distinct cell borders, rod-shaped nuclei and scattered leucocytes.

there is everywhere a definite tendency to acanthosis, even where the elevation of the eruption over the level of the skin is only slight. It is most severe in the nummular and annular forms, while in the flower leaf and circumscribed types it is chiefly found at the edges of the papules. But even the simple scaly spot shows thickening of the prickle layer and mitosis. And, especially in older seborrhœic eczemas, I have been able to determine epithelial proliferation of the coil glands, when the accompanying cellular infiltration of the cutis had reached so deep. It is a remarkable appearance, for we find notoriously, even after excessive functional activity of the coil glands, and in many pathological changes in them, no mitosis in the epithelium,

while, on the other hand, every activity of the sebaceous glands is accompanied by epithelial mitosis. I have examined several seborrhœic eczemas in which every section presented two or three mitoses inside its six or eight coils, but there was no question of a throwing off of the epithelium in large quantity, a sort of scaling—as in the hair follicle. The affected loops of the coil appeared simply enlarged and distended by the mitotic epithelium, which occupies a relatively considerable space. The connective tissue cells in the neighbourhood of such coils showed here and there mitoses, so that the whole gave the impression of a tendency to mitosis reaching the coil from without, not of a growth to repair loss of epithelium.

Apart from the increased mitosis around the coil, the cutis showed in its connective tissue cells no distinctions from other eczemas. But the interstitial œdema is slight; in this also the seborrhœic eruptions tend to dryness. In certain cases free fat in drops and flakes is found scattered all through the cutis, inside the lymph spaces. In well-stained osmium preparations it is shown, not only in larger, regularly-formed black drops in the neighbourhood of the coil gland and the adipose tissue, but also in small drops and fine black granules between the endo- and peri-thelium of the capillaries, up to the papillary body, in the lymph spaces of the prickle layer of the surface of the hair follicle and of the coil ducts; indeed, fat droplets penetrate into the smooth muscles and nerves.

There exists then, without doubt, in these cases, a secretion of fat which is richer than normal and takes abnormal directions; for the normal fat stream of the skin is limited to the route from the coil glands to the sub-cutaneous tissue, its veins and lymph vessels and depôts of fat cells.

Once it certainly seemed to me that, by means of suitable methods, a much more extensive penetration of fat could be demonstrated in the skin in seborrhœic catarrh. I excised in 1887, from a boy with typical seborrhœic eczema, a papule from the back, fixed it with osmium, and took all precautions to preserve every trace of fat. The piece was washed in water and cut into sections without ever touching alcohol, and the sections were mounted in a mixture of levulose (honey) and gelatine. There resulted preparations in which all epithelial structures were almost black with tiny droplets and larger drops. Especially the prickle layer of the surface, then that of the hair follicles, the coil ducts and glands, were beset with these bodies, which, at the first glance, looked like drops of fat. The fibrinous crusts and the collagenous substance were, on the contrary, pretty free. Several prominent histologists, who saw my preparations, assured me they had never seen anything exactly like them. And so I was for a few years

convinced that I had succeeded, in this case, in having proved an undreamt-of richness in cutaneous fat. Unfortunately the preparations remained alone, and though I took much trouble, I was never able to produce another. When I discussed in Paris in 1889 the histology of seborrhœic eczema, I therefore left them completely unnoticed, but since Leloir, convinced that it represented a fatty condition, published the preparations which I had previously sent him, in his and Vidal's "Atlas," I felt compelled to add to the German translation of that work, a representation of marked fatty infiltration of the skin, from a preparation of my former assistant, Dr Török, as one meets it in about half the cases of seborrhœic catarrh of the scalp.

I have since then examined fifty-three cases of seborrhœic catarrh (from the corpse), mounted in the ordinary method after treatment with osmium. (Pityriasis capitis, so-called Seb. sicca, papular Seb. Eczema.) Of these there were eighteen cases of the same extent and severity as in Török's preparation; in nineteen cases there was no fat in the cutis, and in the remainder it was only recognisable in small droplets in the cutis. The prickle layer contained fat in thirty-five cases, and it was often widely distributed. The coil glands, except in five cases, contained fat; in twenty-two there was a large amount.

Whence comes this fat, which we recognise clinically in the greasy feeling of the scales and the peculiar yellow colour? The presence of fat in the cutis, which we have just described, cannot be made responsible for it, for it is seldom present in such a degree, and is often completely absent. Nor is it a general supply of fat, a greasing of the skin elements, but only a varying increase of the normal fat supply from the fatty organs of the skin. It must, therefore, depend on the sebaceous and coil glands. The former, we may clinically exclude as necessarily concerned, since the seborrhœic catarrh with greasy scales is present on the palm of the hand and the sole of the foot. More evident is the demonstration of the histological appearances, which show inside the nummular eruption covered with fatty crusts, the follicles of the lanugo hairs, as well as those of a few long hairs, filled with thickened horny layer, and consequently blocked. Malassez and Piffard showed this in pityriasis, Schuchardt in dry seborrhœa. The sebaceous glands are normal and contain their normal amount of fat, but the secretion is dammed up, and is often arranged on the hair, which penetrates the scale, in the form of a layer of fat, and greases it as far as the scale, where it ceases. Or, if the sebaceous gland of the hair is small, the sebum stops underneath in the follicle neck, and appears to be separated from the hair, and the neck is, as shown by osmium, filled and distended by a not especially greasy, indeed often moist and swollen, horny layer. The sebum may benefit the hair, as it

does normally, but for the fat of the scales and the horny layer around, we must look for another source. If one considers what would be the appearance, if the sebaceous glands supplied with secretion not only the surface of the hair but also that of the skin, there would be evident an increase, a hypertrophy of the gland, since in secreting sebum the cells perish. And we shall find, in the description of the results of the seborrhœic process (Alopecia seborrhoica), that after the falling out of the hair from the open follicles, a true sebaceous seborrhœa is present, along with a sebaceous gland hypertrophy. Still these are conditions which are foreign to the ordinary seborrhœic eczema.

It is certainly not difficult to prove histologically that the fat must arise from the coil glands. Indeed the fat droplets in the gland, which in good osmium preparations can always be seen, are distinctly increased; often there are, as remarked above, in addition to the fat cells, free masses of fat scattered in the neighbourhood. The coils are, as a whole, voluminous, especially those loops which contain mitoses, the lumina of which are always gaping. The sweat pore is also usually strikingly wide. The presence of mitosis in the loops, as in the connective tissue cells around the coil, speaks for an increased activity in them, and harmonises with the increase of the fatty cushion in all old seborrhœas of the scalp, the knowledge of which we owe to Pincus.

Unfortunately these are all only suggestions and indications, for we cannot histologically supply the simple proof which demonstrates the non-participation of the sebaceous glands.

The fatty fluid of the coil we cannot yet follow histologically; we see only that all dry structures which come into connection with it—first, the cuticle of the duct, and later, the horny layer—are blackened by osmium, therefore that all along its way it lubricates those structures. But a method of fixing the fluid in the duct still fails us. But since we can always recognise on the *vola manus* the connection between the fatty drops in the coil epithelium, the fat of the cuticle and the horny layer, and there is no doubt of the existence of fat in the palmar sweat, I regard this, not absolutely complete proof as sufficient in cases of seborrhœic eczema. He to whom it does not suffice, must explain better than we can as yet the separation of the fatty sweat of the palm of the hand. From these, to my thinking, only correct standpoints, the increase of the fat drops in the coil glands suffices to explain the increased fat on the surface.*

The cause of the flow of fat is still less known than the fatty organ. A simple, vaso-motor, functional *hyperidrosis oleosa* we cannot admit, partly because of the structural changes described, which are

* On a typical discharge of fat from the sebaceous glands in old seborrhœa, see under Alopecia seborrhoica.

found within and without the coil, partly because it would not give the skin the yellow colour, which the fat of seborrhœic eczema does. A specific local cause must consequently be present, since the flow of fat is, in many exanthems, exactly limited to the individual eruptions. It is only doubtful whether the morococci of eczema, in addition to a sero-taxis also cause a sebo-taxis, or whether other organisms are to be made responsible for it; to this I shall return later. The view of the flow of fat as a whole, as a chemotactic phenomenon is, however, in my view, the only right one. It would then be clear why it is that the fat is drawn from everywhere outwards, from the coils alone, so long as the sebaceous glands are blocked, and later also from them, and why in some cases the fat wanders through the whole cutis, up to the surface epithelium, instead of following the ordinary upward stream.

As just indicated, the addition of seborrhœa leads to the development of a series of peculiar synanthems, with some of which we are more familiar histologically. In the following pages a number of the more important types of seborrhœic catarrh will be specially considered.

(a). *Seborrhœa simplex.*

Seborrhœic catarrh often begins with a specific yellow colour of the affected skin. Specially disposed to this is the central sweat channel of the face, which runs from the internal angle of the eye, around the nose and mouth, to the chin. On other parts of the body there are also found these primary spots, especially in the flexures of the joints, but here they are run together, and on account of the absence of bright red surroundings, are less striking than on the face. Here also they are now and again accompanied by subjective sensations. Such a yellow colour of the skin is not found in the typical *hyperidrosis oleosa* of the hands and joints. Nor is the yellow skin shiny, as in the *hyperidrosis oleosa* of the face at the time of puberty, but dull, indeed in some places rough and covered with fine scales. Here, there are attacks of intense itching, while, after the scratching off of the scales, a sore feeling and a somewhat reddened spot remains. And thus seborrhœic eczema commences.

I have not yet had the opportunity of examining the primary yellow spots from the face, but they probably show nothing different from the secondary, yellow, healed patches of the flower leaf and annular synanthems. Here the scaling has disappeared, but the transitional zone of cornification and the basal horny layer still show signs of parakeratosis; general widening, increase and paling of the cells, partial disappearance of the keratohyalin, better preservation of the nuclei, and diminished osmium reaction of the basal horny cells. The

remaining horny layer is thicker, closer and more greasy, and to this alone is the dull yellow colour to be attributed. Certainly the examination of the primary yellow spots is of the greatest interest, and it is especially important to discover at this early stage, in which the follicles are not yet plugged with horny layer, whether the sebaceous glands contribute their share to the supply of fat, as they do on the hairy scalp after the hair has fallen out, and what organisms are found in the horny layer in these cases. In scratched-off horny cells I have frequently observed large quantities of the bottle bacillus, but cultivation showed, at the same time, morococci.

(b). *Typus circumcisus.*

A frequent form of seborrhœic eczema on the breast and shoulders is the *sharp circumscribed* form ; circular reddened spots, of the size of a lentil to a pea, flat and rough in the middle, but at the border very neatly limited by a sharp, very fine furrow running round them, which takes the place of a frequently still visible but very fragile, ring-formed, folded, fine crust.

Histological examination shows, in the centre, parakeratosis of the epithelium, or it may be complete restoration of the normal appearance. But at the margin the prickle layer is, in its upper part, spongy, and shows a crust permeated by coagulated serum, or, where this has fallen off, a depressed groove which represents the section of the circular peripheral furrow. Further there is slight dilatation of the blood vessels, no emigration of leucocytes, and hardly any change in the connective tissue cells. Of organisms, along with very few morococci, I have met in two cases with the bottle bacillus and a very fine variety of bacillus in the horny layer, both of the surface and of the follicle.

(c). *Typus petaloides.*

Another graceful synanthem * of seborrhœic catarrh, tending to the ring shape, is the *flower-leafed* form, which also is found most frequently in the sternal region, and then in the inter-scapular. The spots of which it consists show a hyperæmic, somewhat elevated margin, occupying half or two-thirds of a circle, and, at its advancing convex side, sharply margined from the healthy skin, while inwards, towards the open end of the circle, it gradually becomes paler and less elevated, and at the same time presents the specific yellow colour. On the advancing border of the eruption bright red points are usually visible, which are

* The delicate varieties, the miniature examples of our parasitic affections, always indicate a limited vegetation, owing either to the weakness of the parasite or to the unsuitability of the soil.

covered with small crusts, and are equi-distantly arranged. These correspond to the follicles of the lanugo hairs.

There is, in these and in other cases of seborrhœic eczema, no doubt that the affection may develope especially around the mouths of the follicles, though these do not, in the case of the morococci, play the important prominent rôle as they do in connection with the staphylococci, simply because the äerobic morococci develope by no means easily in the neck of the follicle, and never penetrate deeply into it. But here the question of a mixed infection is to be very carefully considered. The bottle bacilli are found regularly and usually in great numbers. Deep in the affected follicles, I have found further very fine bacilli lying in rows in the hair space (length, 0·5μ; breadth, 0·2μ-0·3μ). But morococci were also found, especially in cultures from the scales.

In sections one finds parakeratosis and acanthosis most developed at the follicles of the advancing margin, and from here gradually disappearing in the direction of the opposite healthy side. The spongy condition is here only rarely developed at limited spots, but, on the contrary, epithelial growth is present all over the papule. The cellular infiltration of the papillary body, too, is more distinct than in the other form; the dilatation of the blood vessels is specially present around the follicles.

(d). *Typus nummularis* (*et annularis*).

These two are the most frequent types of universal seborrhœic eczema, and differ from the rounded eruptions of non-seborrhœic eczema, which are much rarer, and from the ordinary nummular areas of psoriasis of the elbows and knees, in the looseness of the scales, their greasiness, the lighter red or yellowish-red colour of the papule beneath, and the tendency of the scales and crusts to leave the border of the papule free. To these types, especially the centrifugally extending, centrally healing, annular type, belong many so-called eczemata marginata, and also many cases of ring-formed serpiginous psoriasis. Where the eruption is general, there is usually, as a predisposing condition, a well-oiled, easily sweating, pale skin, with a well-developed epidermis, but not very thick horny layer, and a well-nourished papillary body, which responds to all lesions with vigorous epithelial growth. The individual patches are usually situated on places which, on the one hand, are in relation to fatty sweat, and on the other are exposed to permanent external pressure or irritation—as the region of the neck, the cruro-scrotal fold, the leg, the back of the foot, the palm of the hand, etc.

In this form, more than in any other, in addition to parakeratosis,

acanthosis is histologically predominant. The infiltration of the cutis is, in the discrete, usually very chronic cases, tenser, and extends deeper than in the generalised forms. Spongy transformation and vesicle formation are only present where specially favourable conditions are added; so, for example, a marginated seborrhœic eczema of the scrotum with typical dry edges, softens, under the influence of warmth, of sweating, or some form of organism in the sweat, in the middle, and then persists as a moist intertriginous eczema. Or a nummular, scabby, seborrhœic eczema of the scalp, which is extending outwards, appears on the forehead as a dry *corona seborrhoica*, and on the cheeks and behind the ears, after removal of the scabs, as moist, fissured eczema.

In the annular type the margin is the seat of marked epithelial growth and parakeratosis; the healed centre is often the seat of a reddish-brown pigmentation, and the yellow colour, which is characteristic of the preceding types, is here more rarely observed. When weeping of the eczematous surface sets in, it is not usually preceded by visible vesicles, the scales are simply thrown off, and the epithelial layers underneath, which have passed through the stage of acanthosis into the spongy condition, no longer permit the formation of scales. Whether crusts are formed, depends on the amount of fibrin in the exudation; this, in the intertriginous forms, is notoriously small.

In cultivating micro-organisms from this type, the morococci are the only constant species I have met with.

(e). *Typus rosaceus.* . *Rosacea seborrhoica.*

This type is the special property of the nose, chin, and cheeks. It was long before rosacea was recognised as part of a general seborrhœic catarrh. This most valuable practical recognition is as easy to demonstrate clinically as histologically. For the histological symptoms, which are most striking in seborrhœic catarrh; the epithelial growth on one side, the spongy transformation on the other, are absent, and in addition to parakeratosis, which tends to slight scaling, it is only an otherwise unimportant symptom, the dilatation of the vessels, which here reaches quite an uncommon degree, and characterises the type. In all slighter cases of rosacea seborrhoica the development of the affection is evident from single lentil-sized, seborrhœic spots, which are scaling or only rough, partly diffusely reddened, or partly covered with ectatic vessels. These are regular outposts of a seborrhœic catarrh of the rest of the head, which, favoured by the habitual vaso-motor paralysis of the arteries of the face, extends to those parts of the face best supplied with blood.

The histology of simple rosacea seborrhoica is still completely

unknown; only injections could give an explanation of the genesis of the changes in the vessels. From this stage I have only examined the scales, and they, in addition to a few morococci, show many "bottle bacilli." But I have carefully examined the resulting stage, the fibromatous growth, which results after long-standing simple rosacea, and the consecutive hypertrophy of the sebaceous glands. This was described by Hebra as *Rhinophyma*, and according as the fibroma or the gland hypertrophy predominates, we have to distinguish two forms. Usually, but wrongly, these are regarded as the results of a simple "acne rosacea"; this definition leads to errors, and must be abandoned. Acne, as we shall see, also leads to hypertrophic conditions (acne tuberosa, acne hypertrophica). But these are typically different from the hypertrophies which follow *rosacea seborrhoica*. In acne we do not need the term of rosacea; *acne pustulosa* and *tuberosa* are sufficient for all consequences. Therefore the mixed term Acne rosacea would be better deleted and replaced by *Rosacea;* this is, in nineteen out of twenty cases, seborrhœic, and only very rarely a simple chilblain-like angio-neurosis, which, by the way, never leads to hypertrophy.

The main distinction between rosacea and acne consists, as the changes in the cutis show, in this, that in the seborrhœic processes only very few plasma cells, and further, no chorio-plaques and giant cells are formed from them, while these cell forms are abundantly present in every long-standing acne. Acne tuberosa is a typical granuloma; hypertrophic rosacea is not. On the contrary, there is here a progressive metamorphosis in two other directions. In some cases fibrous tissue is gradually formed at the cost of the masses of ordinary spindle cells. In pure cases of this fibroma not only does the tissue of the cutis and of the hypoderm pass into it, but there are formed firm, nodular protuberances, especially on the nose, which is, in addition, much deformed. In these cases the coil glands and the sebaceous glands, after the lanugo hairs have fallen out, remain, but the latter do not hypertrophy. In other cases the sebaceous glands increase by the enlargement and multiplication of the lobules, take the form of a tumour, and form the chief part of the rhinophyma, which is dotted all over with transparent areas, and resembles orange peel. In a third series of cases—and these are the most voluminous—both processes are limited to the formation of deformed, lobulated tumours of the nose, and in lesser degree of the cheeks, in which sometimes the fibroma, sometimes the glandular hypertrophy predominates. But even this *Rhinophyma* is a much more uniform and simply-formed tumour than the less prominent acne hypertrophica.

We have seen that the simple rosacea seborrhoica differs from all other seborrhœic processes, in the absence of epithelial growth and

spongy metamorphosis of the epithelium. Instead of this, the great hyperæmia induces a permanent hypernutrition of the cutis. It is only as the termination of these abnormal directions of growth that we find here a hypertrophy of the collagenous and glandular tissue, instead of marked epithelial hypertrophy. The former we shall meet again as a result of seborrhœic catarrh in alopecia seborrhoica of the scalp, the latter is peculiar to the rosacea of the face.

Rosacea seborrhoica may, like any other seborrhœic catarrhs, be conjoined with secondary purulent infection. The furuncles which develope have naturally only a certain external resemblance to acne pustules (*cf.* Acne).

(f). *Seborrhœa capitis. Alopecia seborrhoica.*

The seborrhœic catarrhs of the hairy scalp require a special description, since, in the presence of long hairs and their gradual disappearance, they present peculiarities which are theoretically as interesting as they are practically important.

On various grounds the presence of close, stiff hairs favours the collection of thick scales and crusts, partly because their adhesion to the hairs prevents their artificial removal, partly because each is connected with a collection of horny layer in the follicle, and has, therefore, a sort of root in the scalp. Thick scales and crusts are consequently not, on the scalp, as elsewhere, the result of marked epithelial growth, and when they are removed there does not appear, as in the nummular forms, a cushion of epidermis, but a surface which is dry or moist, faintly or deeply reddened, and depressed rather than elevated. It is well known that the surface of the epithelium of the scalp, in consequence of the epithelium being required for the hairs, is very feebly developed, and, under pathological stimulus, has no great tendency to acanthosis. We have therefore here only those forms which are due to parakeratosis and spongy transformation of the prickle layer. The former leads to dry scales or greasy crusts, the latter to fibrinous crusts. Naturally these conditions are not sharply distinguished, but we can—both in children and adults—pretty well distinguish three forms of skin catarrh, which correspond to three different forms of alopecia.

(α). *Pityriasis capitis* and *Alopecia pityrodes.*
(β). *Eczema seborrhoicum crustosum* and *Alopecia seborrhoica.*
(γ). *Eczema seborrhoicum madidans* and *Alopecia eczematosa.*

(α). *Pityriasis capitis, Alopecia pityrodes.*

We rank pityriasis with the seborrhœas, and not with the simple catarrhs of the skin, with the reservation, that etiological investigation

will, in the future, either confirm or alter this arrangement. The clinical transition of simple pityriasis capitis into the crusted seborrhœic catarrh of the forehead, and the moist seborrhœic catarrh of the ears (and of the face in children), is distinctly in favour of a common etiology; still pityriasis capitis might be a catarrh of other origin which prepares the way for eczema. It is certain that, in addition to a few morococci, one always finds great numbers of the "bottle bacilli" in the scales of pityriasis, not only on the surface, but also in the dilated infundibula of the hairs. Secondly, there is frequently found in sections a very small bacillus, already described under the circumscribed form, and an uncharacteristic, sporeless mould fungus. For the bottle bacilli this is evidently an excellent field for growth. We find them often in numbers, lying closely packed, almost in pure cultures, and can in such cases study not only the development of the club and bottle-shaped, and completely round or oval-shaped forms, from the rods, but also recognise the existence of a thread-like form, three or four times the length of the bacillus, which at one end passes directly into the bottle shape. These are very easily confounded with fragments of true mould fungi.

The entrance of the follicle naturally possesses, in histological relation, the greatest interest, since there we may hope to find the cause of the later alopecia. It is regularly dilated in its whole length, from the surface of the skin to its entrance into the sebaceous gland, by an excessive number of horny layers, which are arranged concentrically around the hair as an axis, in the form of a screw. These reach to the surface and pass into the increased horny layers of the scales surrounding the hair, and are consequently only to be regarded as a regular extension of the anomalous cornification of the surface into the mouth of the follicle. Whether we have at the commencement to do with parakeratosis, and not rather with hyperkeratosis alone, that is, an increased adhesion of the horny cells, is questionable. I have found in more than twenty of these cases, filling the follicle, mostly well-preserved granular cells and horny cells without nuclei; but the power of the latter to take up fat is diminished, and therefore a slight degree of parenchymatous œdema is present.

Thus the follicle at its upper end attains the form of a very broad filter, whose apex ends at the mouth of the sebaceous glands, so that the hair follicle here appears much more hour-glass-shaped than usual. On the hair which runs through, this change has no visible influence, but it frequently affects its root sheath, which is retained in the follicle, and thrown into delicate angled folds. Since it at the same time becomes thicker, and fills up more space between the hair and the epithelium of the hair follicle, the hair in the upper part is

somewhat loosened, but in the lower segment there is no evidence of loosening of the hair. Only, the greater concentric pressure in the upper part of the follicle must in general favour the ascent and the casting of the hair.

It is important that there is no evidence of a stagnation of the sebaceous secretion in or beneath the neck of the hair follicle; nor does the secretion of the glands, as we shall see in other forms of catarrh, bore out a way of its own through the horny masses. The glands are really not much altered at the commencement; in infants, they are normally very small and not prominent; in adults they vary in size, and are sometimes simple, sometimes split into twos, fours, or sixes; in the former they surround the hair on all sides in the form of little bags, in the latter they form a large, lobulated sack, attached to one side of it. They are also filled with normal sebaceous cells, and only one symptom frequently points to an absence of, or a hindrance to, the normal escape of sebum, namely, one finds oftener than usual the lobules completely filled with fatty cells, without any undegenerated epithelium. That is always the sign of an arrest in the secretion of the gland.

These changes, which are readily seen in every pityriasis capitis, by no means explain the result, the alopecia, and yet, as the examination of moderately severe cases—extending from the hairy parts of the head to the hairless forehead—shows, the alopecia follows directly on the first stage of the closing of the follicle. A loosening of the root sheath—as by the penetration of parasites—or an atrophy of the papilla are consequently to be excluded as causes of the alopecia; these cannot be sought in the under part of the follicle, but only in the middle and upper parts. Or in other words: *ordinary alopecia pityriasis capitis depends, not on an atrophy of the papillary hairs, but on their diminished new formation;* for only on that have the upper and middle parts of the follicle any influence.

We find in the first zone of diminished growth of hair the number of papillary hairs diminished, that of bed hairs increased, many papillary hairs in the under part of the follicle surrounded by thickened, homogeneous membrane and loosened, so that in sections it is hardly possible to avoid the removal of most of the hollow roots from the papillæ. Briefly put, there exists, then, a tendency to more rapid separation of the papillary hairs, a more rapid casting of hair, and this is favoured by the increased centripetal pressure in the upper part of the follicle, which tends to raise the hair from the papilla.

In another series of hairs the process extends in another direction, in that the hyperkeratosis, which usually stops at the follicle neck, extends deeper into the follicle, and not only in the middle third

separates the hair sheath from the prickle layer, but at the same time the commencing closure of the follicle. It is a process quite analogous to the hyperkeratosis of the bed of the nail, which, in parasitic affections, elevates the nail plate from the nail bed. Then the neck is dilated, down to the commencement of the under third of the hair follicle, and we now find parasites, mostly small bacilli, but also morococci, growing in the gaping hair space. Still the hairs are seated firmly in the under third in these follicles, since the increased suction, caused by increased concentric pressure, where the neck is closed, is absent.

We find therefore, in a zone lying nearer the bald scalp, three types of hair; papillary hairs loosened from the papillæ, already elevated bed hairs with the under part of the follicle shortened and its sides collapsed, and finally, hairs with widely-opened, distinctly-deepened follicle necks, filled with loose horny layer. And there are also empty follicles, from which bed hairs have evidently fallen out. For they occupy half the length of the follicle, and show, beneath the sebaceous gland region, multiform remains of the lower part of the follicle. There is usually found a small process of old, faintly-staining epithelium, inside a thick homogeneous basement membrane, which is the more folded the more the process is shortened, and which carries, on its under end, a feeble remnant of a papilla. Or a new epithelial process with deeply-staining cells and a few mitoses extends into the old follicle, pushing before it a small but deeply-stained papilla. The characteristic feature of this change of hair, the only one which stamps it as pathological, is *the minuteness of these young epithelial processes.* These by no means correspond to the size of the old follicles, which they should anew supply with hairs, they are about the size of the processes of the lanugo hairs. And if the growth of the follicle epithelium is not favoured by therapeutic means, there develope, in place of the old hairs, only thin hairs of the character of the lanugo hairs, or the process is arrested with the formation of epithelial processes, and no hairs are formed. Thus alopecia begins. It is certainly induced by an increased casting of hair, but this increased falling out of the hair does not lead to baldness; that is caused by the increasing difficulty in forming young hairs. This induces first the growth of spare, thin hairs, and finally, growth is completely arrested.

In the zone which lies still nearer the completely bald scalp we have also three types of hair follicles; bed hairs, with old or young, still unproductive processes, papillary hairs with wide necks, filled with horny layer reaching down to their under third, and completely hairless follicles from which a bed hair has fallen. The more the deep epithelial growth is arrested, the more it extends on the surface; the

surface epithelium becomes almost as thick as the ridge system on the flexor surfaces of the arms and legs, and in connection with it we have here and there a fourth type of hair. There are formed, on the surface, small epithelial depressions, as in embryonic life, which are indented by small papilla, and represent the foundation of a new hair. Certainly they persist long in this stage, and only rarely is there actual hair formation; a scanty replacement of the lost deep hair. The hairless follicles in this zone also present characteristic appearances; they are converted, after the loss of the hair, into lobules of the sebaceous gland. This is chiefly the case in those follicles plugged with horny layer, from which the hair has gone, and they, therefore, form closed sebaceous lobules and, later, regular sebaceous cysts. First, there is stagnation in the lobules of the gland; all the glandular cells become sebaceous. After the available space is filled with sebaceous cells, these commence to degenerate, large fat drops and irregular fat globules escape, leaving behind them the empty spongioplasm of the sebaceous cells; apparently the fat and the empty husk occupy less space than the intact sebaceous cells. As this disorganisation of the cells extends outwards, and the internal pressure at the same time compresses the walls and tends to convert the contents of the lobules into a single cavity, there is finally developed a simple, closed sebaceous sack, filled with free sebum and broken down sebaceous cells, usually still showing at its margins a few glandular remains.

We now come to the completely bald zone of the scalp. Here also there are found one or two well-preserved thick papillary hairs; they are those with widely-opened follicle necks. Otherwise we meet with only a few bed hairs of different calibre; most of the follicles are converted into more or less atrophic sebaceous sacks, or present, so far as they are open, wide spaces, into whose base unaltered sebaceous lobules open; here and there a stunted epithelial process is seen, and the follicles are filled with horny layer, sebaceous cells, and various bacteria. The surface epithelium is thicker than normal, and the papillary body is correspondingly better developed. Small hair germs extend here and there from the epithelium of the surface and the follicle mouths. The coils during the whole process are well developed, and their dilated pores open on the surface. The muscles of the skin are, in spite of the falling out of the hairs, intact; indeed, they often appear hypertrophic; since they have lost their normal attachments they usually assume an abnormally horizontal direction, and distort or compress the sebaceous glands, into which they are now inserted, into unwonted forms. The elastic net is also well preserved. The blood vessels in the upper part of the cutis are always dilated and surrounded by increased and swollen perithelium; the number of mast cells is invariably increased.

The most important change in the cutis is, however, a distinct thinning, which was first pointed out by Pincus. Naturally the loss of the hair and the disappearance of an extensive and rigid mass of tissue is also important; but this falling out is not clinically manifest, since the fatty tissue of the hypoderm is compensatingly thickened, and encroaches on the lower layers of the cutis. Thus the scalp is always becoming less movable, and the prospect of the young epithelial processes producing hairs, less and less.

That, clinically, every pityriasis does not lead to loss of hair, indeed, occasionally not even to increased casting, is explained by the histological appearances. On the one hand, under favourable circumstances, a completely-sufficient aftergrowth may be formed; but on the other hand, in other cases, there is evidently not the tendency to the increased transformation into bed hairs. As, even in excessive alopecia a few papillary hairs with open necks remain firmly enrooted, so it is possible that the majority may also do so, especially when the normal renewal of hair is very slow. This may be the reason why, in women with long hair, the higher degrees of alopecia pityrodes are relatively rare.

(β). *Eczema seborrhoicum crustosum capitis. Alopecia seborrhoica.*

While pityriasis capitis usually affects the scalp diffusely, fatty and inflammatory crusts mostly appear in circumscribed, circular groups. Although the epithelial growth is slight, they consist mainly of scales soaked in fat. The resemblance to simple pityriasis is, in all stages, more striking histologically than clinically, and it is sufficient to draw attention to the few characteristic differences of both forms, so far as they have been investigated.

The earliest appearance of the crusted form is represented by the well-known yellowish, greasy, crumbly scales and crusts in new-born children, which are mostly regarded by their relatives as dirt. Here we find histologically all the features of pityriasis; the scales, the marked dilatation of the follicular entrance by masses of horny layer and the organisms described; only, the hyperæmia of the papillary body is very prominent and the scales blacken more than usual with osmium. The better lubrication of the surface in these very common cases can *only* be explained by the increased coil-gland secretion, for the sebaceous glands of the scalp are at this period very, very small, and, further, do not show the slightest sign of hyper-secretion. Here, as in hyperidrosis oleosa of the palm and sole, the origin of the fat from the coils is easily shown. These are in infants, relatively to the whole volume of the skin, as large as they are in fœtal life, and they end with very definite dilated pores on the surface.

Similar appearances are found in older children, only in them the tendency to marked parakeratosis and to weeping is so great that pure cases are rare (see next form). But it is otherwise at puberty and in adults. Here the tendency to weeping recedes, and that to seborrhœa stands out, and there are many perfectly pure cases in which thick, dry, ceruminous, more or less dark, greasy crusts cover the scalp. Here the appearances are quite different.

The initial stages are characterised by greater osmium blackening of the whole scale. Here also there is, as usual, dilatation and

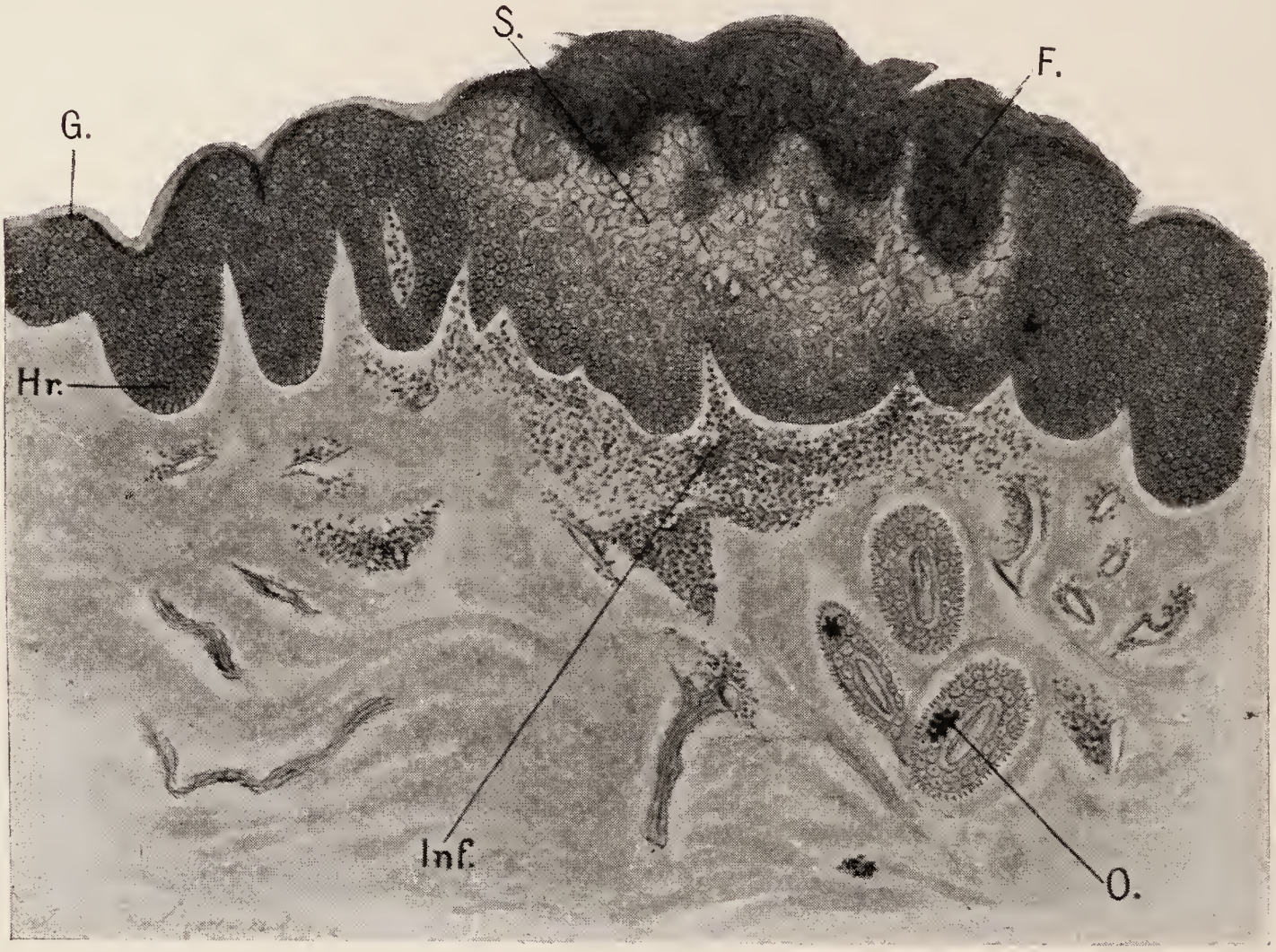

FIG. 8.—Eczema crustosum. Osmium. Hæmatein.

Inf. Cellular infiltration of the papillary body under the crusted eczema vesicle.
Hr. Hypertrophic ridges of the prickle layer.
G. Granular layer developed around the vesicle, but absent in its immediate neighbourhood.
S. Spongy state of the prickle layer passing outwards into the eczema crust, which extends downwards with fibrinous coagula (F.).
O. Fatty drops blackened by osmium.

plugging of the hair follicle necks, and it is quite evident that the coil gland fat more completely lubricates the scales from below upwards, being excreted in increased quantity. But as the process advances, there is also an attraction of the sebaceous gland fat, which is visible, inside the follicle, in the form of a cylinder of fat near the hair shaft. We must call it an *attraction*, for the soft fat worms through the horny layers which close the entrance of the follicle in the form of a sausage, and

appears, instead of in its normal distribution on the hair, in a coherent layer on the surface of the skin. In contrast to the coil fat, it is not at once sucked up by the horny layer, but remains rather by itself, and is caked together into masses. If the scale formation goes further, we frequently find layers of fat between the scales, and almost always the oldest sebaceous excretion on their surface. Corresponding to this general sebo-taxis, the sebaceous glands are, in contrast to pityriasis, hypertrophic, for these glands, unlike the coils, cannot provide an increased secretion, without increasing in size. As the hairs disappear, they assume even greater dimensions, and finally occupy, as in the glandular form of Rhinophyma (rosacea hypertrophica) the greater part of the cutis.

Of organisms, the "bottle bacillus" is found here abundantly, but is not so predominant as in pityriasis. For this seborrhœic form is, beyond all others, the haunt of organisms. We always find considerable numbers of morococci in the upper layers of the crust, but in the under layers and in follicle necks are various forms of bacilli, both the frequently mentioned, very tiny bacillus, a larger form about the size of the tubercle bacillus, but plumper, and finally, deep down in the sebaceous gland, pure cultures of a very delicate, slender, usually somewhat bent bacillus, which is present in irregular collections, and in this resembles the acne bacillus. Here also the future must teach us which organism, and especially whether one only, is the cause of the accompanying sebo-taxis.

The development into alopecia and the cause of this are the same as in pityriasis capitis. Only, in place of the simple cylindrical and barrel-like horny cysts with atrophic glandular lobules, there are similar fatty cysts connected with very voluminous glands. The complete filling of the glandular lobules gives them a more regular form, since they do not, as in the functionless glands of pityriasis, suffer distortion from the cutaneous muscles. As in the glandular form of rhinophyma, the fatty cysts of the hairless follicles on the surface often recall clinically the transparent appearance of orange peel.

The other appearances of the affection are the same as in pityriasis. The alopecia here also, in spite of the increase in volume of the sebaceous glands, leads to thinning of the cutis, with accompanying hypertrophy of the subcutaneous fatty tissue. The cellular infiltration is equally slight, the dilatation of the vessels on the surface usually rather more marked.

(γ). *Eczema seborrhoicum madidans capitis. Alopecia eczematosa.*

In every moist eczema of the head in infants, the gradual extension from the forms just described, especially the dry seborrhœic,

may be observed. But histologically the seborrhœic character is completely concealed by the important changes of the epidermis, which the weeping leads to. There is developed, in contrast to the previous forms, marked epithelial proliferation of the surface, and much more marked serous and leucocytic exudation in the cutis. Consequently we find here all the appearances which characterise the severely weeping eczema of adults, in other parts of the skin; œdema of the papillary body, swelling of the epidermic ridges, parakeratosis of the margin of cornification, heaping up of the nucleated horny layer into scales, a few inter-cellular vesicles of the prickle layer, and then

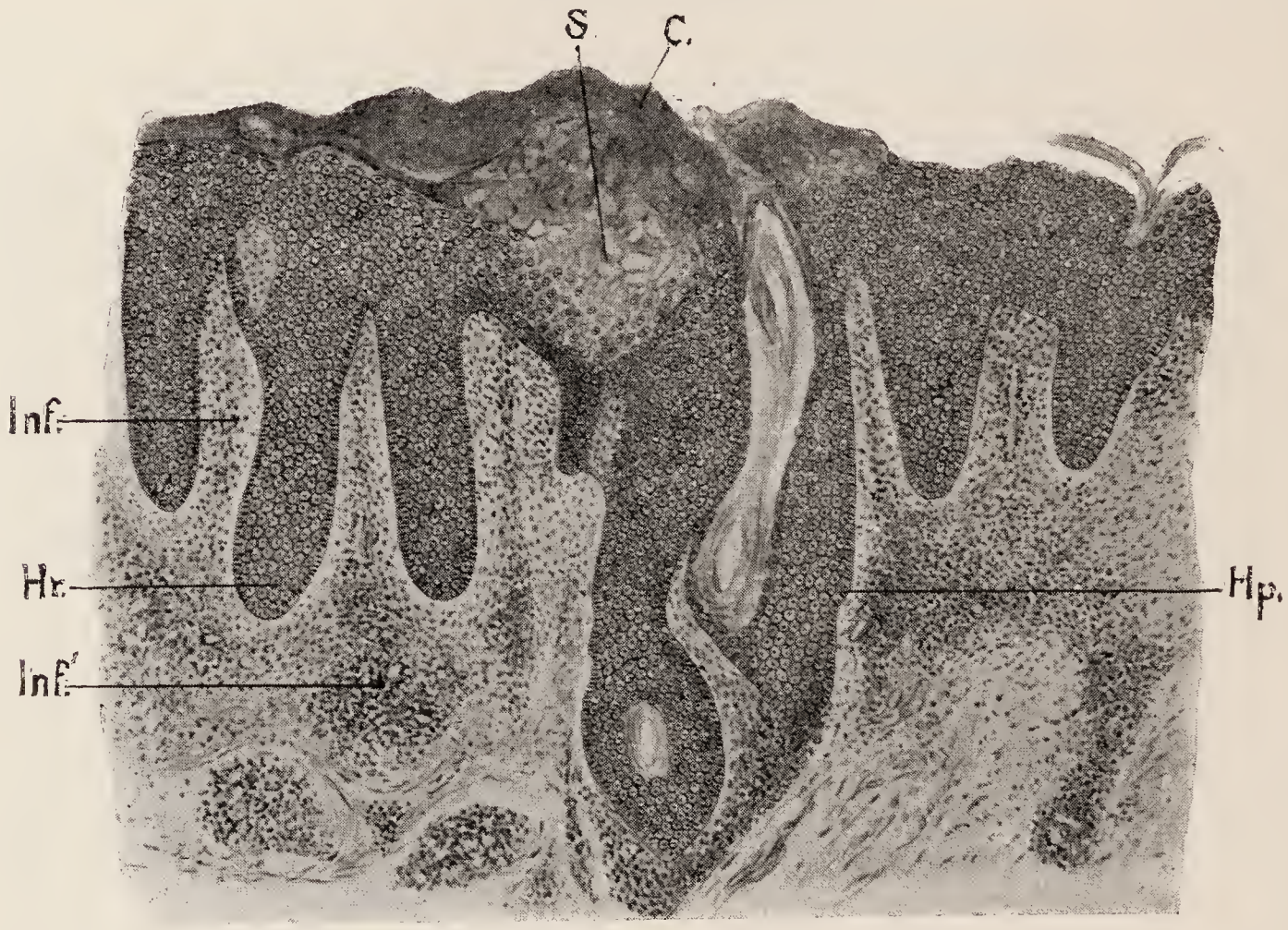

FIG. 9.—Eczema crustosum. Alcohol picro-cochineal.

Inf. Cellular infiltration of the papillary body.
Inf.' Cellular infiltration of the sub-papillary vascular net.
Hr. Hypertrophic ridges of the prickle layer which pass directly into the horny layer without any granular layer.
Hp. Hypertrophy of the prickle layer of the follicle.
S. Spongy transformation of the prickle layer at the side of a hair follicle, passing outwards into a sero-fibrinous crust C.

its complete transformation into a spongy tissue, with the formation of smaller and larger fibrinous cavities in the scales, which continue to soak up exudation and give origin to especially thick fibrinous crusts, which are usually incorrectly described as "impetignous." At the same time, there is all along present the same dilatation and plugging of the follicle neck as accompanies dry seborrhœa.

Infantile eczema is distinguished by three circumstances from the corresponding form in adults; first, the marked acanthosis of the surface epithelium, which is completely absent in adults, then the admixture of more numerous leucocytes in the secretion, and—perhaps in connection with this—the multiform "flora" of the crusts. The mulberry-shaped groups of morococci are nowhere so luxuriantly formed as here, the larger, older colonies fill the superficial parts of the crusts, but some diplococci are found even in the undermost layers. In addition there are found bottle bacilli, very small bacilli, and in many cases streptococci and many other organisms.

In no case does the moist eczema of infants lead to other than a transient loss of hair. The specially luxuriant epithelial growth makes this impossible. Many eczemas never lead to an increased falling out of hair. After the weeping has ceased, there frequently remains a dry seborrhœic catarrh, in which the morococci recede in favour of the bottle bacilli, and the lubrication by the coil secretion again sets in.

Progress in seborrhœic catarrh in adults takes place in the same way as in infants, by slow stages, but in much more limited degree. The differences of the two have been already noted. The normal atrophic epithelium of the scalp of adults is never the seat of striking growth, and the eczematous crusts are here seated almost directly on the a-papillary cutis. The crusts are firmer, contain less serum than in children, and very few leucocytes; their "flora" also are more uniform; large beautiful collections of morococci are found almost alone. On the other hand, the seborrhœic appearances do not disappear so completely as in infantile eczema; the crusts sometimes pass into diffuse fatty scales, and show here and there a mixture and contamination with evident sebaceous secretion.

From this it is evident that the moist seborrhœic eczema of the scalp differs strikingly from that of other parts of the body in adults. With the epithelial growth, the primitive inter-cellular vesicles are absent, and naturally there is no spongy degeneration. The whole prickle layer, down to a few of the lowest layers of cells, becomes parakeratotic, and is converted almost completely into a fibrinous crust. The serous œdema of the cutis and the dilatation of the blood-vessels is much more marked than usual, as is the increase and swelling of the perithelium. The follicle necks are widely open, partly filled with horny layer, partly, in addition, with fibrinous exudation; the hairs are rapidly transformed from the papillary into the bed hair stage. But the mitotic new formation of epithelium, which takes place more readily in the prickle layer of the hair follicle than in that of the surface epithelium, provides for the regular renewal, so that in

general the moist form of catarrh does not lead to persistent alopecia. Certainly, in very long-standing eczemas, the prickle layer of the hair follicle suffers and the renewal is delayed, but it always sets in when the disease is cured. Evidently, also, the more marked scaling of the surface epithelium, in the moist form, interferes with permanent plugging of the follicles, and therefore with the formation of those horny and sebaceous cysts, which in most cases prevent the new formation of young hairs, and in the later stages of pityriasis and dry seborrhœa play so great a *rôle*. Hypertrophy of the sebaceous glands and of the subcutaneous tissue does not set in, even in long-standing moist eczemas, but in cases of more marked alopecia there is thinning of the cutis. In a case (Gabel) in a young girl, there were found, along with acne, in different parts of the head, the dry and moist forms of seborrhœic catarrh. Here the "flora" of the differently formed crusts had an exceptional and extreme luxuriance, such as is only usual in the moist eczemas of the head in children; there were found morococci and bottle bacilli in large numbers, and small bacilli in the crusts, hair follicles, and sebaceous glands, and yet there were absolutely no new and strange organisms. In spite of the multiformity of the flora of the scales in these affections, it is in general much more uniform than is usually supposed; there are many *individuals* but only a few *varieties* of organisms, which are constantly repeated in different combinations.

(g). *Typus exfoliativus malignus. Pityriasis rubra seborrhoica.*

There are severe cases of universal seborrhœic eczema, which, after lasting for years (especially in old people), finally lead to death, with the appearances of *Pityriasis rubra*. The individual spots disappear, for new ones are constantly appearing and uniting with the old to form a continuous diseased surface: and thus gradually the whole of the skin is affected. If this condition of general epidermic thickening, constant profuse scaling, and sporadic weeping is accompanied by severe itching, it may lead rapidly to loss of strength, and the patient dies after three to five years of debility. If the itching is not marked, strength is longer retained, the disease may last for ten years and more, and pass into a second, atrophic stage, in which the characteristic histological symptoms of the first stage disappear.

The first stage of the malignant exfoliative condition is characterised chiefly by a peculiar retrogression of the earlier, flat, papular eruption. While the surface generally presents, without distinction, a parakeratotic epidermis and thick scaly elevations, we find here and there, on closer observation, under this altered surface, areas of the

epidermis and the papillary body in the form of flat elevations, which represent the remains of an earlier, nummular, crusted seborrhœic eczema. The diffuse cellular infiltration of the corium is limited to about its upper half and stops very abruptly; the cutis, in addition to its richness in ordinary connective tissue cells, is distinguished by marked dilatation of the blood vessels, and the presence of more or less yellow pigment. Outside this the cutis is again almost normal. In this hyperæmic and pigmented lower margin of the infiltration we recognise the much-changed superficial vascular net of the cutis. The papillary body above is also markedly thickened by the increase of collagenous —not elastic—substance, and a considerable collection of spindle and round connective tissue cells, along with a number of mast cells; plasma cells are not present. Compared to the normal, the collagenous tissue of the papillary body is thickened, without the admixture of fine threads, and swollen into faintly-stained homogeneous bands (partial hyalin degeneration). The papillæ have become club-shaped, and the ridge system between them is correspondingly thin, so that a section shows a series of fine epithelial columns inside these slightly-swollen areas, which are connected over the thick papillary heads like arches. With ordinary nuclear and protoplasmic stains these ridges appear to be sharply margined at their ends, and the prickle layer also is clearly defined over the apices of the papillæ. But if we use a collagenous stain (acid fuchsin, picric acid) we see at once that the epithelial columns extend by homogeneous yellow flakes, easily distinguished from the red collagen, which penetrate the cutis in the same direction as the epithelial columns. Many of these cords, consisting of flakes, are united in the form of a net, others are detached from the under margin of the prickle layer over the apex of the papilla, and penetrate more or less into it. When one has studied stained preparations of these flakes, and convinced himself that they represent simple colloid degenerated epithelium of the old ridge net, he can find them again on sections stained with ordinary stains, since, on shutting off the light, their refraction makes them evident. They are often somewhat displaced in section, and consequently lie loose by one another in the old tracks of the hypertrophic epithelium. Nuclei can no longer be recognised in them; the whole contents are converted into an oval mass of a greenish-white colour and mother-of-pearl shimmer. All these degenerated structures entangled in the swollen papillary body are, when the section is not properly stained, readily confounded with the surrounding swollen collagen. They have a not unimportant share in preserving the volume of the papular elevation.

The existence of this colloid epithelial degeneration explains, in a simple way (as in Ulerythema centrifugum), how, in many limited

spaces, the connection between epithelium and cutis is loosened, and spaces and fissures appear, filled with serum or fibrin. The changes of the epidermis, above these papillary remains, are otherwise the same as over the free skin lying between. The prickle layer is extremely thin, consists, at most, of four layers, on which there is a parakeratotic, widened transitional layer, and a coarse, lamellated, heaped-up horny layer, which always contains the same organisms; morococci and bottle bacilli. In limited spots even the last fragments of the prickle layer undergo this colloid degeneration, so that, with a nuclear stain, it appears as if the horny layer lay directly on the cutis. Where there are no remains of the papule, the papillæ have disappeared with the last epithelial ridges, and on a hyperæmic, smooth, slightly-infiltrated cutis, lies a minimal prickle layer and a markedly thickened, fissured horny layer. The follicles of the lanugo hairs disappear with the sebaceous glands, owing to the constant separation of epithelium; the coil glands are at first well preserved.

These appearances explain the main symptoms of this type; the hyperæmia, and persistent scaling, while the colloid degeneration of the epithelium explains the transition into the atrophic stage.

Properly preserved preparations of a somewhat earlier stage would certainly show a relative richness in epithelial mitosis, which is not evident in my preparations; the extraordinary persistent scaling certainly requires this.

The second, atrophic stage of the disease developes from the first by increase in all the regressive, and arrest of the progressive symptoms. The sub-epithelial infiltration of the cutis almost disappears, the epithelial processes undergo complete colloid degeneration, break down, and then disappear by slow absorption of the fragments, the dilated blood vessels become narrower, if they do not actually go back to the normal; but especially degenerated is the collagenous tissue of the lower cutis, which small, refractile, globular and rod-shaped parts of the coarser bundles, and later, larger parts of whole bundles, show to have become colloid. At this stage the coil glands also suffer; some of them perish from atrophy. The epithelial formation on the surface diminishes, and instead of the thick, horny scales, a thin, shiny, parakeratotic horny layer covers the minimal prickle layer.

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(*c*). Leucofibrinous Inflammations.

Impetigo leucofibrinosa (*leucofibrinous bleb.*)

H., boy aged ten years. Duration of disease four years. On the extensor side of the thigh and on the buttock there appeared, at varied intervals, groups of large, sometimes round, sometimes irregularly formed purulent vesicles. They began as small pustules with deep red margins, extended more in breadth than in height, and were covered with thick, brown, loosely adherent crusts.

A moderately large, fully-developed bleb showed a distinct formation from three different layers. The actual cavity, the middle layer, is flat and mono-locular, filled with leucocytes and a fine fibrinous net. It is covered by a still broader, much swollen layer of the cover of the blister, which has developed by the entanglement of great quantities of fibrin and leucocytes in the pre-existing horny layer. At the periphery of the blister this spongy covering is at its maximum, and then, diminishing, passes directly into the horny layer of the surrounding epithelium. The base of the blister consists of the prickle layer, depressed by the vesicular contents; it is, however, densely permeated by leucocytes and thready fibrin, and is consequently markedly swollen. The fibrin forms in many places a continuous, narrow-meshed net, which contains in its meshes sometimes unchanged epithelium, sometimes well-preserved leucocytes. In other places the fibrin is less, partly granular, or like myelin drops, but always extending through the whole prickle layer of the vesicular base. But the most striking fact is, that the entanglement of fibrin in the prickle layer stops short at the cutis margin. The cutis and papillary body contain no fibrin. This, then, has evidently formed from a fibrinogenous albuminoid of the exudation, in combination with a derivative of the epithelial cells. But these are no more destroyed than their nuclei, and have certainly not become fibrinoid. The papillary body is packed with leucocytes, as far as the sub-papillary vascular net. Outward from this, the emigration of white blood corpuscles is more scanty; only the vessels themselves are surrounded by sheaths of leucocytes. The whole cutis, but especially the papillary body, is œdematous, the lymph spaces are wide. The

collagenous tissue is well preserved, the elastic has only partly disappeared in the neighbourhood of the papillary body. All the blood vessels of the cutis are dilated, even those at some distance from the vesicle. In the papillary vessels the emigration of leucocytes is partly indicated by the formation of white columnar thrombi, especially under the margin of the vesicle. The epithelium around the vesicle is swollen and œdematous, and thus, without the formation of mitoses, the ridge net round about the blister is distinctly thickened. This œdematous, prickle layer with its wide lymph spaces, passes, towards the middle, into the prickle layer of the base of the vesicle, whose lymph spaces are filled with fibrin instead of serum. There is a tendency of the fibrinoid prickle layer to elevate itself completely, here and there, from the œdematous swollen papillary body.

The contents of the vesicle are formed of leucocytes, serum, and fibrin, but the latter is much more sparingly present than in the epithelial sheath margining the vesicle, the covering, and the base. The vesicle has no relation to sweat pores or follicles.

The development of the blister is evidently to be ascribed to the entrance of particular organisms, which are found only in its central part, in the much loosened spongy covering. They lie here in clustered groups and have the form of small cocci. Stained with the pararosanilin - iodine method, they now and again give the impression of short, thick, almost oval rods, still it appears to me that they are more correctly regarded as diplococci; for, with a very high power, one can resolve them into two neighbouring cocci, which are separated by a faintly stained septum, and held close together by a common membrane. Certainly they are by their form and somewhat smaller size (diameter of single cocci, $\cdot 3\mu$ - $\cdot 5\mu$) easily distinguished from the ordinary pyococci. They evidently divide slowly; hence the rod-like diplococci. Other organisms were not found.

The distinctive characters of this affection are, in addition to these organisms, the richness of the exudation in fibrinogenous substance and leucocytes, the œdematous character of the cutis and the epidermis at some distance from the blister, and the saturation of the covering and base of the blister with coagulated thready fibrin. It forms the type of leucofibrinous inflammation of the epidermis.

Impetigo multilocularis (the many-chambered pustule).

S., a man aged 31. Has suffered for some weeks from an eruption of purulent vesicles on the face and hairy scalp. The vesicles are mostly the size of a mustard seed, but run together to larger polycyclical, pretty persistent blebs; they have a yellow colour and are flat, the larger ones are mostly covered with

brown crusts, or are already completely dried. The vesicular coverings are compact, the crusts of the older ones firmly adherent. The surroundings are reddened. The first vesicles were found on the left temple; from here they extended over the whole forehead, both cheeks, and the back of the nose, extending towards the right. The affection was probably caught from some domestic animal.

I have several vesicles of this peculiar eruption. A perfectly fresh one shows the commencement of the process, in the form of a circumscribed loosening of the prickle layer, distinct dilatation of the inter-spinal lymphatics and profuse permeation with leucocytes. Under this œdematous epithelial papule, which occupies the space of about three papillæ, the cutis is closely beset with leucocytes as far as the sub-papillary vascular net, which is sheathed by wandering cells. But the nature of this leucocytosis is peculiar. It strikes one at once that the nuclei of the white blood corpuscles are almost all stretched out and converted into bent, stretched, angular threads, as they otherwise appear here and there, artificially, at the dried-up corners of a preparation. The leucocytes streaming from the sub-papillary vessels towards the papule therefore frequently indicate the seat of the lymph-track. In the somewhat flattened papillæ found underneath the papule, and still more in the œdematous increased papillæ in the neighbourhood, the leucocytes are not equally arranged, but collect themselves in larger quantities in the lymph spaces around the capillary loops. By their extended form and parallel arrangement they give the impression of bundles of closely-packed rods, which have been bound together and fitted to the angles of the lymph spaces. With a low power these collections appear as streaked, leucocytic, perivascular thrombi, of hollow cylindrical form, filling the greater part of the papillæ.

The whole appearance points to an interference with emigration. The leucocytes must evidently adhere very closely to the walls of the lymph spaces in order to acquire this elongated shape and to form such dense thrombi. Possibly there is also an absence of simultaneously exuded serum; for the œdema of the epithelium is limited to the middle part of the eruption, and the papillary body shows no œdema.

The older eruptions show the corresponding appearance of a multilocular abscess-formation in the epidermis, and thus the affection differs from ordinary impetigo.

There are usually grouped around one or two main vesicles a few larger sub-vesicles lying beside them, and a whole series of very tiny vesicles enclosed in the covering. Consequently there is no uniform vesicular cover, but, according to the position of the sub-vesicles, it consists in one place of simple horny layer, in another of compressed

areas of the prickle layer; and frequently the smallest vesicles are enclosed in it. This compound vesicle also extends in varying depths into the papillary body; there is no regular base. Usually, even in the main vesicles, a remnant of compressed prickle cells forms the base; on many places this is very much thinned or completely broken through, and the impetigo extends into a small abscess of the papillary body. In the same way vesicles lying above or near each other frequently run together, and there develope in this way, hour-glass or biscuit-shaped larger vesicles. The resistance of the epithelial cells forming the walls in this extension of the epidermic abscesses is characteristic; they are pressed upon, separated, and greatly deformed, but there is no colliquation or any other kind of necrosis.

The cutis under the epidermic vesicles is, in its upper half, though only in definite lines, permeated by leucocytes. But at the height of the affection all the blood vessels are much dilated. Leucocytic thrombi are found here also in a few papillary lymph spaces at the periphery, but as the process advances most of them are re-dissolved. The papillary body underneath the main vesicle is always depressed. At the periphery of the eruption there are found, according to the position of the sub-vesicles, stunted, diminished, normal, or enlarged, œdematous papillæ. This irregularity of the papillary body is still further increased by two forms of degenerative processes, which are found more or less developed in all preparations; these are small abscesses, and a diphtheritic change in that part of the cutis directly in contact with the epidermis. The development of the small dermal abscesses is the same as that in the epidermis; they are dense collections of leucocytes in surroundings relatively free from leucocytes, which apparently originate in a stagnation of wandering cells inside an obstructed lymph track. Some of them lie exactly at the margin between epithelium and papillary body, and approach the deeper epidermic abscesses, here and there uniting with them. Others occupy the middle part of the papilla, dilating it in a globular way and pushing the blood vessel aside. Only a few are found at the under-margin of the papillary body. When they lie in the connective tissue, the collagenous tissue is locally rarefied, and has often shrunk to a few fine fibrillæ. In many places the pus from the cutaneous abscess has formed a way to that of the epidermis, so that there are formed larger abscesses constricted at the middle, reaching from the cutis directly to the horny layer.

But still more remarkable is a peculiar coagulation of the uppermost edge of the cutis, at those places which are penetrated, but not permeated, by leucocytes. The fine irregular fibrillation of the connec-

tive tissue is here replaced by the dense homogeneous structure of a strongly refractile, shining mass, which is everywhere broken up by cavities, and is difficult to stain. In the interstices are seen the naked nuclei of the leucocytes and a few connective tissue cells. With a good fibrin stain, certain parts of this lattice-like, coagulated and swollen part of the cutis take the stain, as is usually the case in croupous and diphtheritic membranes. Otherwise they behave, in appearance and staining, exactly like the diphtheritic surface of the cutis after removal of epithelium, *e.g.*, in soft diphtheroid chancres; the peculiarity is, that here the same appearance is present in epithelium, still preserved, though beset with vesicles.

Apart from these degenerated parts, the collagen is everywhere well preserved; but, on the contrary, the elastic tissue inside the inflammatory parts is diminished and stains badly. The epithelium around the vesicles is quite normal, not œdematous, and shows here and there mitosis.

The vesicles chiefly contain well-preserved leucocytes and a small quantity of fibrin. Only in a few superficial sub-vesicles is this relation reversed; much fibrin with few leucocytes. There are no loose epithelial cells in the vesicles; it is a simple displacement vesicle; the marginal epithelial walls are smooth, sharp, and never swollen.

From the whole clinical and histological relation there can be no doubt that we have here, as in ordinary impetigo, a parasitic affection of external cause. But with the means at our disposal no micro-organisms could be recognised.

This Impetigo multilocularis is, in distinction to the ordinary Impetigo staphylogenes, a leucofibrinous inflammation, with a tendency to diphtheritic degeneration of the cutis and the formation of a multilocular vesicle.

Pemphigoid exanthem. (Leucofibrinous vesicles with colliquative necrosis.)

One case (a young girl), remarkable, because the chronic bullous universal eruption recurred year after year. The patient had been treated for "universal pemphigus" in many hospitals. She came under my care with apparently the same dermatosis, but now limited to the neighbourhood of the genitals.

A vesicle the size of a pea, from the thigh, showed a simple, pretty flat, vesicular cavity, covered by a very thick top, consisting of the epidermis, elevated as a whole. The base of the blister consequently was formed of the œdematous, swollen papillæ, stretching naked into the cavity. The cutis beneath was very œdematous; all the lymph spaces were dilated to their maximum; the connective tissue cells were increased, some contained two nuclei and a little deeply-staining

protoplasm, but there was no formation of plasma cells. The blood vessels were moderately dilated, the mast cells not increased. Leucocytes permeated the cutis in considerable quantity, and were collected in the cavity of the blister, where they were surrounded by horizontal, partly net-formed fibrinous cords, and together with these and a quantity of serum constituted the contents of the vesicle. The formation of the cover differed in the centre and in the periphery; the middle part was somewhat more extensive than the peripheral segments, and consisted of the much-swollen horny layer, which is later dried up into a thick fibrinous crust, from whose under side hung very much altered remnants of the prickle layer. The two peripheral segments of the cover are of younger date, and evidently represent a secondary zone of extension of the vesicle. They consist of the whole cutis without a layer of crust, but they show noteworthy changes. One can still definitely distinguish the ridges and the indentation of the epithelium, corresponding to the summits of the papillæ. Especially at such places many collections of epithelium have undergone colliquative necrosis, protoplasm and nuclei do not stain, and the epithelial margin is blurred. More rarely there are found single epithelial cells in the middle of the ridges, which have become homogeneous and do not stain; since these epithelial clumps are at the same time much swollen, they compress the neighbouring epithelium, which is arranged concentrically around them. On the central, crusted part of the covering, the epithelial ridges dependent from it have undergone complete colliquative necrosis, so that it is only with difficulty that one can distinguish them from the equally badly-stained contents of the vesicle.

Of organisms, the eruption appears to contain in abundance only one variety, which, in size and arrangement, resembles the morococcus of eczema. They form diplococci, sometimes in long rows, sometimes in fours and larger packet-shaped groups, which closely permeate the crust, and at its centre penetrate in considerable quantities into the blister. Here they lie, often in fours, inside the leucocytes, and are distributed sometimes in them, sometimes singly and free, all over the vesicle. It is important that single ones may be found in the peripheral corners of the younger zone of vesicles, and that they lie free, consequently cannot have been conveyed by leucocytes. This circumstance—as well as the tendency to the formation of fours and packets—indicates that we are dealing with a special and specifically active form of coccus.

Ecthyma. (Willan-Vidal.)

Discrete large pustules with a deep red halo and a hard base, which dry up into dark-brown crusts, and leave behind them distinct scars, thus differing from all impetigo pustules. They are inoculable and auto-inoculable; the inocu-

lated pustules reach their acme on the fourth day, and correspond exactly to the form of the inoculation (Vidal). The pustules, so long as they are not deprived of their horny layer or otherwise dried, extend concentrically, undermining the horny layer, and may reach the diameter of six centimeters. Their seats of predilection are the leg, buttock, the fore-arm, and then the rest of the trunk. Cachexia and convalescence from febrile diseases predispose to them ; but they are also found in quite healthy children.

According to Leloir, the pustule formation begins in the prickle and granular layer with the "altération cavitaire," *i.e.*, the expansion of the peri-nuclear zone of the epithelial cell and the formation of inter-cellular elementary vesicles, which run together into larger cavities and spaces by rupture of the cell walls, become filled with fibrinous fluid and pus, and finally form epidermic abscesses. In the coarse meshes of the epithelial net there is found a finer fibrinous reticulum. The papillæ under the pustules are densely infiltrated with leucocytes, are, in their centre, flat and broad, and at their periphery, elongated and hypertrophic. Sometimes the ecthyma pustules become hard from lymphangitic œdema, and then resemble syphilitic scleroses. They are not infrequently localised in a hair follicle. The contents of the pustule dry up into a brownish crust, under which the underlying purulent fluid sometimes forms a new crust, which raises up the old one. By an extension of this process a rupioid crust may develope. In three cases of hæmorrhagic ecthyma, Leloir recognised, in the cutaneous vessels, endarteritis and endocapillaritis. In four cases of ulcerative ecthyma (two cachetic adults, two marasmic children) this vesicular lesion induced a necrotic process of the papillæ and the superficial cutis. Then Leloir found in five gangrenous ecthyma pustules, in addition to the staphylococcus pyogenes, bacilli, and he regards the different forms of ecythma as the expression of different degrees of invasion of specific—still unknown—micro-organisms of ecythma into the epidermis and the cutis. Cultures from ecythma pus produced staphylococci and streptococci, with which he was no more successful in inducing true ecythma pustules than other authors with the organisms which they isolated. (Du Castel : spores ; Mathieu and Netter : chain cocci ; Baudoin and Wickham : streptococci ; Ehlers : Bacillus pyocyaneus.)

I had recently the opportunity of examining two typical cases of Vidal's ecthyma, of one only the pus, of the other, pus, crusts, and a pustule excised on the fourth or fifth day of its existence : both were in children.

The pustule came from a two-and-a-half-year-old boy, who had suffered from the disease for eighteen months. The affection began with an eruption like chicken-pox, which in a few days extended over the whole body. Under various treatment the pustules frequently healed, but always reappeared.

Now, the legs, buttocks, and back of the trunk are occupied by

pustules, with hard red and grey pigmented borders. Between them are seen superficial white scars; the legs are especially covered with them.

The removal of a crust from a spot on the sacrum, which was at its height, showed that it passed directly into the epidermis of the surroundings and left behind it an oval, flat, pretty even loss of substance, covered with pus. The crust was of an almost equal thickness. Microscopically it consisted of three layers, which were more evident in methyl blue glycerine-ether mixture, than in picro-cochineal-gentian-violet-iodine preparations. The uppermost layer is the old horny layer, richly beset with fibrin, the middle contains many leucocytic nuclei and a lesser number of epithelial nuclei, which have all taken a notched and angular form from the close packing of the coagulated fibrin; it is formed by the prickle layer, saturated with leucocytes and fibrin. The undermost layer is a dense mass of pus, with well-preserved pus corpuscles and without fibrin, which can only be followed here and there a short distance into the layer of pus, from the old epithelial margin, in the form of a fine net or thicker clumps. Only the uppermost layer, consisting of horn and fibrin, contains any special organisms. These are pretty large cocci, which are present in rows and masses, especially in the centre. They have a longish form, and are usually about $1{\cdot}25\mu$ in long diameter; they are therefore somewhat larger than the staphylococcus aureus. But they are further distinguished from it by the regular form of the masses. They do not lie together, extending in many directions, forming clusters, but, as very fine and well-stained sections show, in almost parallel rows, so that each collection actually represents only a number of adjacent rows. But, on the other hand, the arrangement in rows is not so pronounced as in the streptococci, in particular there are no bent single rows, nor do the cocci lie close to one another, but are regularly separated by an unstained edge (thus differing from pyophoric strepto- and staphylococci). Diplococci are rarer than short rows. None are found in the leucocytes.

On the ground of these histological peculiarities, and the circumstance that only this one form of coccus is present in the crusts, it is permissible to suspect in them something specific and etiologically important, and, therefore, I have gone more closely into them. But I must note that in sections of the pustules I could not find these collections of cocci, but found only scattered, uncharacteristic cocci. The pustule evidently showed an earlier stage of the eruption; it did not show the greenish-yellow colour of pus, but the pure straw yellow of epidermis permeated by fibrin: it was elevated above the level of the surrounding skin, distinctly depressed in the centre, and sur-

rounded by a dark red, broad halo. The sections show that the inflammation reaches, in the central part of the ecthyma pustule, through the whole depth of the cutis, for the collagenous bundles here are widely separated by an inflammatory œdema and a large quantity of leucocytes, as they are in the neighbourhood of a staphylogenic abscess. But no abscess has formed, for the collagenous bundles are only softened and loosened, not run together and destroyed. The paths of the leucocytes are the lymph tracks of the cutis itself, they are equally distributed, and not specially collected around the hair follicles or the coil glands. At the periphery, corresponding to the red halo of the pustules, one finds the blood vessels dilated and the leucocytes migrating towards the middle part of the pustule; the leucocytes are consequently chiefly arranged perivascularly.

In the papillary body the inflammatory œdema is peculiarly distributed. In the red marginal zone it is penetrated by wide capillaries, and is somewhat œdematous; but nearer the centre the capillary hyperæmia diminishes, and the œdema distinctly increases, so that the pustule is directly surrounded by a wall of extraordinary broad and much swollen papillæ, between which the epithelial ridge net is reduced to minute depressions. In relation to the pustule itself, the œdema again diminishes, and corresponding to the external depression completely disappears in the centre.

On the epidermis, also, several concentric zones can be distinguished. In the outermost, corresponding to the red halo, there is found an œdematous swelling of the epithelium, and also considerable inter-cellular œdema. This inflammatory œdema goes on, above the zone of the severe papillary œdema, partly to reticular degeneration of the prickle layer, partly to complete colliquation of the protoplasm. The completely, or previously reticulated, liquefied cell bodies run together, so far as they are not dissolved, into homogeneous bundles, which do not take up basic stains, and acid ones only faintly, but mostly have well-preserved nuclei, poor in chromatin. There is then, in the ecthyma pustule, a definite arrangement—like the anthrax pustule—an epithelial system of cavities above a papillary one; both contain strikingly few leucocytes. Further towards the centre, in the outer part of the pustule itself, the serous exudation rather suddenly gives place to a fibrinous one. All the layers of the epithelium are permeated by firm coagulated fibrin, and thus are converted into a homogeneous mass with the fibrin reaction, beyond which, however, the peripheral œdematous zone extends. Thus developes the elevated wall of the pustule, compared to which the centre, relatively sunken, appears as a depression. In the centre itself, where the pus from the cutis reaches the epithelium,

the latter is certainly coagulated, but the voluminous admixture of fibrin is absent, as is the great œdema of the peripheral zone. One might expect to meet here, at the navel of the pustule, the specific organism inside the epidermis. But I have not, either with methyl blue or iodine, been able to discover it. One sees on a few sections, in the centre, the leucocytes making their way from the cutis to beneath the coagulated epithelium, and may conclude from this that the pus corpuscles, in constantly increasing numbers, gradually collect under the firm coagulated crust, flatten it out, and there is first formed the pustule proper, whose covering I have already described from an older pustule.

From this it is evident that the ecthyma pustule differs importantly from the staphylogenic impetigo, in this, that sub-corneal suppuration, an epidermic abscess, is not directly developed, but the suppuration appears secondary to a characteristic inflammation of the epidermis, which is, at its centre, purely fibrinous, and at its periphery very œdematous in character. Thus the ecthyma pustule has a certain resemblance to the variolous processes, in which also epidermic degeneration precedes suppuration. The drop of pus in the ecthyma pustule consequently sits deeper in the tissue, it is not sub-corneal, but sub-epithelial, and extends in the papillary and cutaneous tissues. Thus we see how the ecthyma pustule, if not mechanically injured, shows little tendency to burst, although now and again the sub-epithelial drop of pus bursts into the œdematous marginal zone, and then the crust acquires a peripheral wall of pus (rupioid transformation). The flat, somewhat depressed crust, with its large amount of fibrin and its triple layers, also differs importantly from the impetigo crust, which consists of pure horny layer and dried-up pus. Further differences are the extensive inflammatory hyperæmia in the surroundings, the marked œdema and the scar formation. The latter is—as in variola and acne varioliformis—not to be attributed to a direct destruction of the papillary body, but to its flattening out beneath the firm fibrinous crusts and to long-continued pressure, which leads to an epithelial adhesion at an abnormally deep level, and to a permanent depression of the surface. The process never leads to a necrosis of the surface of the cutis. The clinically evident pigmentation around the ecthyma pustule corresponds to a considerable amount of pigment in the basal prickle layer of the outermost zone, where the prickle layer commences to swell.

The discoveries as regards bacteria in the pus in both cases were, as is easily explained from the secondary character of the suppuration, negative.

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(*d*). Purulent Inflammations.

Impetigo staphylogenes, Pustular blcb (Bockhart).

By staphylogenic impetigo, I understand, rapidly appearing, superficially lying vesicles, which, from the commencement, possess yellow, purulent contents, and are surrounded by either none or a small hyperæmic halo. If complications are absent (Acne, Furuncle, Eczema, Dermatitis, etc.), the base is neither inflamed, degenerated, nor œdematous. The size of the impetigines varies from that of a turnip seed to that of a pea, a bean, or larger. They may at once show their definite size, or extend in the course of a few days. But they almost always increase in height, and thus remain semi-spherical and never show a depression. They cause no subjective sensations, and dry up, after a half to two weeks, into a brown flat crust, which, after falling off, leaves a slight depression, but no scar. In other cases a deeper suppuration of the skin is developed (furuncle). The number of pustules is unlimited ; from a single one a universal eruption may develope by scratching, etc. The localisation is also unlimited ; the predilection areas of impetigo are arranged according to the frequency of the irritants leading to them ; the inoculation of staphylococci may induce them. For the same reason the times of predilection are the periods of healing of eczema, small-pox, chicken-pox, etc., persistent purulent affections of another kind (ulcers of the leg, eczema) or other form (furuncle, sycosis). Much rarer than the appearance of widespread secondary impetigines, is the primary uncomplicated outbreak of many impetigo pustules, and it is always attributable to special infections.

The pure form of impetigo pustule is best studied on the smallest mustard seed spots. These present a uniform typical appearance, which is altogether distinguished from that of other, secondarily purulent vesicles, *e.g.*, chicken-pox. In the large pustules, especially in those with liquid contents, there may appear certain changes, which are also common to other processes.

The pyococci, which have penetrated under the horny layer, increase so rapidly and lead to such rapid collections of pus locally that, even in the smallest visible pustule, one finds the horny layer separated from the prickle layer, the latter being flattened and pushed convexly into the cutis. The interspace is occupied by a closely-packed mass of pus cells, which enclose, singly and in groups, a few uncornified but otherwise well-preserved epithelial cells. It has the form of a bi-convex

lens, expands the horny layer outwards and the papillary body inwards, and on the second day is twice or four times as thick as the whole epidermis. The uppermost layers of the prickle cells are flattened by pressure like the horny cells, but are otherwise unchanged. The horny layer during the course of the disease is little disturbed, and is only elevated as a whole, and thus the sweat pores are usually torn, and are only preserved at the lateral parts of the pustule, where they are sometimes very much stretched.

The most important and interesting discovery in these pustules is that of the pyococci. If we examine the inside of the elevated horny layer of small pustules in well-stained preparations, we see that it is covered in its whole extent by staphylococci, singly or in swarms.

From here they extend in the well-known clusters, rapidly increasing in size, and, as a whole, pretty regularly distributed through the pus, to close on the base of the pustule; they do not, however, penetrate into the underlayers of the epithelium. They are most closely packed where the pustule is shallowest, where it runs into the granular layer of the neighbourhood; then in certain parts of the pus, in the upper layer more than in the under, they are collected into larger clumps; and in the centre of the horny covering, the starting point of the eruption, one frequently meets compact masses of micrococci.

But this method of distribution changes regularly with the age of the pustule, even on the third and fourth day. The increase in the cocci does not keep pace with the collection of the pus corpuscles, and there gradually collects at the base of the pustule a broad layer, relatively free from cocci, marking off the upper zone, which usually contains cocci, from the healthy cells of the base of the pustule, and thus leading to the encapsulation and healing of the pustule. In all the older and larger vesicles the cocci are chiefly found, only directly under the horny layer and in the adjacent parts of the pus. Neither at the commencement nor later have I found cocci inside the pus corpuscles of epidermic abscesses, nor in the detached or marginal epithelial cells.

In view of the statements of different authors, especially of the most recent worker on staphylococci, Kronacher, I have carefully studied a large number of pustules, and have come to the definite conclusion that the staphylococci only grow outside the cells. Since it is difficult to get sections of abscesses sufficiently thin, I got Dr Walker to examine, in my laboratory, the pus from several sycosis patients, daily and methodically; his investigations only confirmed my view; neither the pus nor the epithelial cells ever contained cocci. The arrest of the growth of cocci in the course of pustulation consequently does not depend on Phagocytosis.

Whence the pus cells arise, is easily seen in many pustules, since one finds the base of the pustule, although never very richly, everywhere permeated by wandering cells. But it is very remarkable that some pustules are margined underneath by epithelium which contains very few wandering cells, and these are large pustules, which have deeply depressed the prickle layer and papillary body. I have often, in such cases, made an observation which may suffice to explain this paradoxical appearance. I found the sweat pores, penetrating the prickle layer, frequently dilated and filled with wandering cells, which empty themselves into the pustule, while in the neighbourhood there were only very few leucocytes.

Possibly, as the pressure of the pustule on the tissues beneath increases, the wandering cells adopt this method of exit. There was never in these cases any penetration of the cocci into the sweat pores, and I was never so fortunate as to be able to follow, even from the densest layers of cocci on the surface, a single one into the sweat pores. But it certainly appears as if the chemotactic action of the cocci was able to attract the wandering cells through the sweat pores.

There is no separation of fibrin in the smaller and rapidly healing pustules. But with proper staining one sees beautiful fibrin spirals between the epithelial cells directly surrounding the pustules, and also in the lymph spaces of the cutis. Herein lies the proof that the purulent inflammation, like every other, permits the escape of fibrinogenerators out of the vessels, but their action, immediately around the cocci, possibly owing to the peptonising qualities of the latter and the leucocytes (Leber), is suspended. Numerous mitoses in the epithelium are found in the neighbourhood of the pustule, during its acme, and a slight, wall-like thickening of the epithelium about the pustule cannot be denied. Underneath the pustule the papillary vessels are moderately dilated, and discharge a—usually very small—number of wandering cells. Otherwise the cutis presents nothing abnormal. In general, in almost all impetigo pustules, there exists a remarkable contrast between the slight appearance of inflammation beneath the pustule and the great quantity of pus in it, especially when one compares with it processes like Variola and Zoster. There takes place here a simple attraction out of the vessels rather than any notable injury of them.

The simple, small impetigo pustules, just described, heal up by the uppermost epithelial cells of the pustule becoming cornified, and thus converting the abscess into a crust. At the same time there appear numerous mitoses in the prickle layer of the base of the pustule, which elevate the base and favour the loosening of the crusts. These,

if properly stained, show in their upper parts sometimes single cocci, sometimes groups. Indeed, where the compressed mass shows cracks, these are sometimes found filled with small pure cultures of cocci, the proof that the cocci by no means necessarily die in the course of pustulation, and that, in general, they find better conditions of nutrition in the indifferent crust, than previously under the influence of the living epithelial and wandering cells. Certainly we must always regard the impetigo scabs, as inoculations show, as eminently infectious.

The course is somewhat different when the growth of the staphylococci rapidly diminishes under the influence of the leucocytic wall, and their attraction of pus consequently ceases. Then the impetigo does not always immediately dry up, but may even increase by further transudation. But this is now only sero-fibrinous. The pus is thinned, and the leucocytes sink down or, separated by serous fluid, swim in the vesicle like large balls. The pyococci, which adhered closely beneath the cover of the pustule, can consequently be more regularly distributed in the vesicle. The base of the pustule also changes its character; the compressed prickle cells, which tend to cornification, are considerably swollen. Thus the uppermost layer of the base of the pustule becomes too large and is thrown into folds, which, in the sections, are seen like festoons in the pustule. These swollen epithelial cells have become partly fibrinous, although their nuclei are preserved, and they show between them fine nets of fibrin. In many detached collections of epithelium there now developes that form of dropsical swelling, which I have named ballooning. Here and there we find multi-nuclear balloons, as in the variolous processes. But there is never any reticulating degeneration.

The healing of these liquid, flabby pustules takes place in the same way as I have described in the tense, purely purulent pustule. This whole ante-finem modification is only to be regarded as a tendency of the impetigines to fibrinous inflammation, which is induced in long-standing cases by the relative weakness of the coccal growth. It is not that a fibrinous inflammation developes into a purulent one, but to a primary, and, on account of its origin, purely purulent inflammation, there is often added an apparently fibrinous stage. We will more rightly regard these occurrences, according to the above observation, simply as an escape of the fibrinogenerators into the pustule, contemporaneous with the diminished virulence of the coccal poison.

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Impetigo herpetiformis.

This pustular disease, as described by F. Hebra, is almost limited to pregnant and lying-in women ; it is localized mainly and chiefly in the genito-crural region, but extends from here over the whole body, and also to the mucous membranes of the mouth, and with severe general symptoms (fever, rigors), almost always leads to death. According to Kaposi, the eruption is chiefly characterized by the fact that the lesions **appear** as pustules. They are superficially arranged in groups and extend circularly, new serially arranged pustules on an inflammatory base appearing in the neighbourhood of the groups, while in the centre cornification sets in, either immediately or after temporary weeping. The pustules never ulcerate or form scars.

According to Du Mesnil, whom we have to thank for two careful examinations of a case of Impetigo herpetiformis, the assemblage of leucocytes begins, in the smallest vesicles, in the most superficial part of the prickle layer. As the pustules increase, the horny, granular, and part of the prickle layer are elevated in order to form the cover of the pustule, while the base is formed from the considerable remnant of the prickle layer. This is closely beset with leucocytes, which, with a few epithelial cells and a small quantity of serum, form the contents of the pustule. In a few of the larger pustules almost the whole prickle layer is elevated as the cover of the pustule, so that only a few cylinder cells still clothe the naked papillæ. These are œdematous and closely beset with cells, while the papillæ of the erythematous halo only show cellular infiltration around the papillary vessels. The marked cellular infiltration of the papillary body, and the upper layer of the cutis, is sharply marked off in a straight line from the under. As far as the infiltration reaches, the blood vessels and lymph vessels and spaces are dilated. The blood vessels here and there show endothelial swelling of the intima, widening and cellular permeation. The hair follicles, sebaceous and coil glands Du Mesnil found intact, only the lumen of the latter was dilated, as were the adjacent lymph spaces.

In the condylomatous growths, which appeared in the course of the—otherwise favourably terminating—case in the inguinal region, there was found marked acanthosis of the inter-papillary, not of the supra-papillary prickle layer, dilatation of all the superficial blood and lymph vessels, dense cellular infiltration, and considerable œdema of the papillary body.

In the pustules cocci were evident, sometimes isolated, sometimes in groups between the leucocytes, and a few were inside the infiltrated zone of the cutis. In view of the septic termination of the disease, an extension of the infectious agent from the eruption into the circulation is probable, and special attention should be directed to this in the future.

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Dry Catarrh of the Skin.

Psoriasis.

If one understands by psoriasis an eruption consisting of small, very reddened circumscribed spots or flat papules, running together to equally reddened, more or less elevated patches in which all the eruptions are covered with loose, white, silvery scales, on whose removal small drops of blood ooze out, then the histology of the affection is easily described, although so much that is contradictory has been written about it. From the not specially qualified reader it must not be concealed that those contradictions partly depend on the fact that the diagnosis of psoriasis is by no means so simple as would appear from the ordinary definition just given, and that the different investigators must have had before them very different looking spots and papules. There is probably only one region of the body, that of the elbows and knees, where the eruptions almost always have the psoriasis type mentioned above.

But there are not only regional differences for the different descriptions of these authors ; there comes into consideration the fact that it is by no means easy in every case to separate psoriasis from an equally wide-spread disease—seborrhœic eczema—and very frequently psoriatic papules pass into squamous, crusted, or even weeping, seborrhœic ones. Their gradual transition is found especially on the face and hairy scalp.

We must leave it to the future to decide whether that which we still call psoriasis is only an extreme, very well characterised type of the same catarrh which appears on other persons and on other regions as seborrhœic catarrh, or whether they are only allied and combined dermatoses. Whichever it be, the familiar and venerable type demands its right to histological explanation, and our description will not be misunderstood, if we previously declare that it applies, not to everything which has been called psoriasis, but only to the above-defined, extreme, dry "elbow" type.

To a certain extent we depart from our plan, and consider the literature of psoriasis more than that of other diseases. This is—especially compared with the very scanty literature of eczema—astonishingly large, and, further, is well fitted to place in the clearest light, to what contradictions the methods everywhere used must lead ; pieces are cut out without reference to the clinical aspects, and the stage which they represent, without regard to their genesis, and without appropriate variance of the methods of examinations, and these are calmly described as typical of the whole affection.

As in the psoriatiform seborrhœic catarrh, the basis of the change in this psoriasis type is in two factors—**parakeratosis** and **epithelial growth**. To these two main changes there is added a third—**dilatation of the vessels**. This latter is also evident in the corresponding forms of seborrhœic eczema—and thus these become "psoriasis-like"—but is not so fully developed.

Even the smallest, punctiform psoriasis spots show the three main symptoms in different combinations. At the very commencement parakeratosis is always present, and shows itself as a simple thickening of the horny layer, or as a heap of scales. But there is immediately added to it, either epithelial growth, and there develope small, pale, scaly papules, or dilatation of the vessels, so that the spots assume an intensely red colour, and are covered with scales, right up to the edge. But in both cases the third missing factor is soon added, and the complete psoriasis papule is formed.

Thus we see that the simple parakeratotic area developes in two ways—by that of the *pale papule*, or of the *red spot*. The older Hebra and his pupils (Neumann, Kaposi) laid more weight on the latter method of development, and regarded it as typical of psoriasis. And since the red colour sufficed to indicate an inflammatory, or "a change comparable to inflammation" (Hebra senior), the doctrine that psoriasis was an inflammation of the skin arose from this clinical view. With one or two personal restrictions, in addition to the above authors, G. Simon, Duhring, Cornil, and Ranvier, among others, adopted this view.

The absence of all acute signs of inflammation (pain, local hyperthermia, fever) aroused contradiction to this view, and drew attention to the development from a pale papule, and to the explanation of the secondary hyperæmia, as a simple not an inflammatory, congestive or stagnatory hyperæmia (Wertheim). Naturally this view could also be well supported by those histological pictures in which the epithelial growth was prominent. The complete indefiniteness of the histological criteria of "inflammation" lightened the criticism of the theory of inflammation, and so it was not difficult for Robinson, Jamieson and Auspitz, with much apparent right, to remove psoriasis from the large group of inflammations of the skin.

So long as one demands, in chronic inflammation, the same criteria as in acute, viz. (in addition to the redness), pain, heat and disturbance of function, one is certainly justified in not putting psoriasis with the inflammations, in spite of the redness and the cellular infiltration of the cutis, which is always evident histologically. But since for us the diagnosis of inflammation is already supplied by the chemotactically attracted exudation, and since it may be either parenchymatous or interstitial, every disease whose main change is parakeratotic is also an inflammation.

But admitting this, we certainly do not need, as Kaposi does, to regard the parakeratosis as the result of a primary inflammation of the cutis, and to find proof of this in the redness. Parenchymatous exudation of the epidermis and dilatation of the vessels are rather

co-ordinate actions of the same cause; the same parakeratosis which is present in psoriasis, we find in other dry forms of the seborrhœic catarrh, without any marked dilatation of the capillaries. And if one must construct a relation between these changes, parakeratosis, as clinical observation teaches us, certainly always precedes the redness, while the second epithelial change, acanthosis, accompanies the redness only in some cases, and in others follows it.

We see from this that the two theories of inflammation and of epithelial growth, accompanied by dilatation of the vessels, do not exclude one another, but that the main histological facts are recognised, by microscopical examination during the clinical course, as parts of a uniform process. So is it with the so-called parasitic theory of psoriasis, which is not opposed to the other, but whose histological basis—namely, the discovery of cocci in the horny layer, for us the most necessary accompaniment—is the first link in the chain of the other appearances. We therefore find the very earliest changes in the immediate neighbourhood of the horny layer, as an œdema of the transitional layers, as in eczema, only of lesser degree.

Unfortunately the sparcity of the morococci in the horny layer in psoriasis makes their recognition, in sections, not impossible, but a very serious undertaking. But here there are available other methods of examination, the somewhat less troublesome, direct proof from squash preparations of the horny layer, and the always successful indirect one, on sections of removed horny layer which has been preserved aseptically on nutrient media. If sufficient precautions against infection from without are taken, and the inoculation taken only from the undermost layers of the scale, a pure culture of morococci grows abundantly at the body temperature on nutrient agar.

The more uniformly this latter discovery points to the parasitic origin of psoriasis, the more certainly that view appears to be confirmed, which assumes in the healthy psoriasis skin a peculiar predisposition to the eruption, though certainly not in the sense that any sort of irritation can induce psoriasis, as was believed possible before the parasitic era in pathology. But the healthy skin of psoriatics presents a nutrient medium of a peculiar sort, which gives to the eruptions induced by the irritation of the parasite, a special stamp. The long-noted peculiarity of the skin of psoriatics found its scientific explanation in the well-known experiment of Köbner and its results, that superficial irritation of the horny layer during the outbreak of universal psoriasis had, about a week after, as a result, the appearance of small psoriasis nodules in the streak. One sees at the first glance that there is scarcely an experiment which so closely resembles a successful inoculation, it being admitted that the infectious agents are widely distributed in the horny layer.

Wherein this peculiarity of the skin of psoriatics (in contrast to the skin of eczematics) consists, I have already indicated in describing the eczema psoriatiformis, so nearly related to psoriasis. It consists on the one hand in a weaker tone of the vessels, which, under injurious influences, readily permits increased blood pressure in the capillaries of the skin, and on the other, in a firm epidermis which resists the serous exudation.

After these general explanations we now turn to the histological details, and commence with the parakeratosis. This expresses itself, here as everywhere, in the complete or almost complete disappearance of keratohyalin, and further of eleïdin from the basal horny layer. Hand in hand with this goes the retention of a larger remnant of the nucleus than normal, and a larger mass of stained remnants of protoplasm between nucleus and horny membrane. None the less are the cells of the scale cornified; their covering resists acid peptic digestion. But they are not so completely cornified as the normal horny layer, since during life they remain moist and soak up less protective fat from the coil glands. Consequently they swell up more easily by imbibition, since they retain a considerable amount of protoplasm. Further, in virtue of their greater moistness, they yield better to the surface tension, do not break off so readily, and are consequently heaped up in large lamellæ; in scales. After the healthy, old horny layer on the affected part is thrown off, it is replaced by an abnormal horny layer, much thicker and constantly thickening, which no longer shows the sub-division of a stratum lucidum (basal horny layer), a middle and superficial layer, and is consequently quite uniform. Only two things disturb the regular conformation. On the one hand, the air from without enters irregularly, after external drying has led to fissures. The more that takes place the more does the scale reflect the silvery colour. On the other hand, there comes from within, by increased exudation, a greater number of leucocytes into the prickle layer, and these are found, after the cornification of the epithelium, arranged in it in rows. Whether all the nuclear fragments are derived from leucocytes, or whether some areas are developed from a breaking up of the epithelial nuclei, must be left to special examination. I believe the latter probable.

The disappearance of the granular layer in the formation of the scale was first noticed by Suchard, and it certainly sounds remarkable, in connection with this readily observed condition, that other investigators find the granular layer normal (Vidal and Leloir), and others again speak of its being three or four times thickened (Neumann). And yet these facts are correctly observed and only incorrectly explained; they relate to a further stage of the scaling, where the scale is

being again elevated by a young granular and horny layer. In this stage, one may find, underneath the parakeratotic horny layer, a specially broad granular layer; later, even a broad granular layer, followed by a small basal horny layer, and over that the scale. One finds in most pieces of psoriasis, places joined to scales, as well as with merely adherent scales. In the former case the keratohyalin has almost disappeared; in the latter, it is excessively developed by the slowing of the process of cornification.

The widening of the stratum lucidum, described by Loewe, does not take place in any stage; the scale is not merely a widened, but otherwise normal basal horny layer, but it is a pathologically altered one. As, except for the drying-up, it retains the rest of its structure, one may call the scale a pathologically altered basal horny layer. And naturally there can be no question of an independent growth of this stratum.

Rindfleisch has already correctly attributed the white colour of the scales to an abnormal quantity of air. Leloir draws attention to the fact that, after removing the scale, in addition to the marked amount of blood, the absence of refracting granular cells favours the red colour of the papule.

As in regard to the granular layer, the views about the prickle layer and papillary body are very contradictory. The increase of the papillæ and the dilatation of the papillary vessels was already observed by Wertheim, who, restricted by the then pathological views, sought for the latter phenomenon some stagnatory cause in the circulation. As if any kind of circulation in the capillaries of the skin could have had as its result a local, circumscribed capillary dilatation! He did not think of a circumscribed arterial paralysis, such as, in lesser degree, every inflammation involves.

That the papillæ are really much enlarged is seen in every horizontal section of the papillary body. For this we no longer consider the distance of each individual layer from the surface. The view that this was due to an active papillary growth into the epithelium has been completely dissipated by Auspitz with his new view, according to which the great lengthening of the papillæ is the result of epithelial growth into the cutis. As a fact, an enlargement of the papillæ does take place, partly by a slight cellular increase, partly by a not-inconsiderable œdema, but mostly through the increased blood pressure acting directly on the capillaries. But all this would only lead to thickening and clubbing of the papillæ, while we find them enormously drawn out, but of their original thickness, thinner, or rarely thicker. The increase in length is consequently constant, the thickness varies much. It is, therefore, quite certain that we have rather to do *with a deformity* than with the simple increase in volume of the papillæ.

This deformity is found mostly in the substance of the older papillæ, but is not limited to them. Where the pre-existing papillæ are low—as in the face—by the same process of epithelial growth parts of the horizontal plate of the papillary body are bent into the papillæ, or new papillæ are first excavated out of it—as, for example, regularly on the almost a-papillary hairy scalp. Where the original papillæ are pretty large, they are usually only lengthened, with a corresponding loss in breadth. Where the papillary body is œdematous, the form of the papilla, under the pressure of the growing ridge system, often does not remain cylindrical, but, on account of the regular fluid pressure, tends to assume a globular form, and thus becomes pear-shaped, with a somewhat contracted base.

The epithelial growth and the simultaneous deformity of the papillary body follow the law laid down under eczema, and since the resistance of the horny layer is considerable, and the papillary resistance maximal, we naturally have a maximal inter-papillary prickle layer, and a minimal supra-papillary one. On the thinness of the latter, and the nearness of the head of the papilla, depends the bleeding when the scales are removed.

Of the changes in the connective tissue, the most interesting is the relation of the blood vessels. Injected preparations of psoriatic skin shew changes of their calibre of the same nature as those of the papillary body. If we follow, from the healthy skin around, the superficial vascular net and the capillaries of the papillæ, up to the border of a psoriasis papule, we see at once that all these vessels are a little increased in thickness and length; they are, therefore, somewhat more twisted than usual, but are otherwise normal, that is, they ascend obliquely inside the papillary body. At the border of the papule itself, where the epithelial growth and the stretching of the papillæ begin, the vessels also, since they constantly increase in length and thickness, become stretched and assume a more vertical direction. The capillaries of the papillæ now arise at greater distances, parallel to one another, and perpendicularly from the superficial vascular net, which has a horizontal direction, just as they normally do on the palm and sole. But we at once see a striking difference between the arterial and venous capillaries. The excess of blood in the psoriatic skin is solely to be attributed to the account of the venous capillaries and veins. These are, in injection preparations, most strikingly dilated and twisted, while the arterial capillaries are only a little wider than normal and somewhat stretched. Thus we can distinguish, more readily than usual, the two sides of the peripheral circulation. The arterial capillaries of the papillæ elevate themselves perpendicularly from the horizontal, only slightly dilated arteries of the upper net, and

usually divide so as to supply two or three neighbouring papillæ. Arrived at the apex of the papillæ, they become wider in their lumen, and increase so much in length, that in place of one upper vascular loop, there developes a double or triple bow or a regular knot, which occupies the place of the uppermost part of the descending venous limb. Then follows, at a point somewhat further on, usually in the middle or in the under third of the papilla, a somewhat sudden, considerable widening of the lumen of these capillary veins, which at once again assume a straight course, and appear in the neck of the papilla as a wide tube beside the much narrower tube of the arterial limb. From the union of these wide venous capillaries there now develope the very ectatic veins of the upper vascular net, which at once attract attention in all injected preparations of psoriasis skin. Further on, in the deeper vascular net, the difference between arteries and veins is by no means so marked; both are slightly dilated. The capillaries given off to the coil glands do not share in the dilatation, the venous capillaries of the coil glands and fat lobules are of normal calibre.

To put it shortly, there follows on a moderate general dilatation of the vessels in the psoriasis papule, *an excessive dilatation of the venous roots* of the descending limb of the papillary capillaries; and further, there is added at the papillary loop a *quite unusual lengthening* of the vessel *for a short distance*, which is the cause of the regularly developing formation of loops. The elongated vessel has no room in the capillary, and is thrown into folds (loops). It is, I believe, beyond question that this form of vascular dilatation cannot be attributed alone to an arterial paresis and increased blood pressure, but that for that part of the capillary system lying next the epidermis, that is, for the papillary loop, there must be added a special factor which induces stagnation of blood (chemotactic), which first lengthens the vessels and then dilates them. This is, especially in relation to psoriasis, not to be lost sight of.

The other appearances in the cutis do not differ importantly from those present in the psoriatic stage of eczema. The cellular infiltration is mostly in the immediate neighbourhood of the blood vessels, and does not extend beyond an increase and swelling of the ordinary connective tissue cells. There is usually found around the coil glands some slight cellular infiltration. Plasma cells are only singly and very rarely present. In the œdematous connective tissue of the papillæ, where these are swollen and pear-shaped, there are usually found a few large connective tissue cells, without much granular protoplasm —on the contrary, with basket-like dilated spongioplasm. Mast cells are always present, but only in moderate number. Leucocytic immigration is not a part of the pure type of the psoriatic papule here

described. Certainly one finds here and there limited immigration in the papilla and the epithelium ; where this is present, the type passes into that of the psoriatic form of eczema, other changes setting in in this direction (diminution of the dilatation of the vessels, &c.).

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Pityriasis rosea Gibert (Pityriasis maculata et circinata, Duhring).

A sub-acute eruption of delicate rosy-coloured spots and flat papules, which are arranged symmetrically, chiefly on the sides of the trunk and the region around the large joints (sides of the neck, the chest, under the axillæ, inguinal regions, and thighs), rarely on the arms and legs, almost never on the exposed regions of skin (face and hands). There is usually, for one or two weeks, a primary spot of somewhat larger dimensions on one of those places (Brocq), after which the eruption developes somewhat suddenly. The spots are somewhat elevated, rosy red, irregularly margined, become depressed in the middle, and extend to a diameter of 2 cm., while they are covered with a fine, firmly-adherent scale, and take on a somewhat yellowish (fawn) colour (Pityriasis rosea maculata). On the predilection areas they run together into large irregular patches. A few spots continue to increase concentrically, and after complete healing in the centre, look like rings (Pityriasis rosea circinata). Only the petaloid type of seborrhœic eczema can possibly be confused with pityriasis rosea. In it, however, the red colour has a yellowish tinge : there are, on the borders, dark red erosions or crusts, corresponding to the mouths of the follicles, in the healing centre, scales are absent, the patches almost always

extend eccentrically, and leave behind them a saturated yellow colour; while further, in that form, one can always recognise the connection with eczematous spots of some other variety (eczema seb. capitis, pityriasis alba of the face, etc.).

My material comes from two typical cases—an adult and a boy, who were under my care at the same time. The former showed the highest development of pityriasis rosea, for the spots in the centre were a good deal elevated above the level of the skin, and some of them presented very fine, just visible vesicles. Two papules were excised from each patient, and together they presented a series of uniform changes. Since the distinction of the macular and circinate forms only depends on the more rapid central healing and peripheral extension of the latter, and histologically possesses no special interest, I prefer to divide the material into that of the *macular* and *papular* eruptions, that is, to describe a *lesser* and *greater degree* of the same.

A scarcely elevated, small, rosy red spot, covered in the middle with a rough surface, showed a pretty marked thickening of the prickle layer, which is only partly to be attributed to a parenchymatous swelling of the prickle cells, partly to regular epithelial proliferation. One finds a striking number of mitoses in the germinal layer, and the epithelial ridges are consequently a good deal enlarged. This hypertrophy of the ridge net is very irregularly distributed over the affected surface—in contrast to the regular hypertrophy in seborrhœic eczema; we find numerous advancing epithelial ridges close beside quite normal ones. The follicular entrances and their immediate surroundings especially share in this acanthosis, but the process is by no means purely follicular. To these symptoms in the prickle layer there is added an inter-epithelial œdema of the lower prickle layer, which is at once definitely pronounced; leucocytes are only present occasionally in the dilated interspinal tracts, or altogether absent. Towards the centre of the spot we find a change in the upper prickle layer which favours and explains the scale formation which ensues. While on the young peripheral parts of the eruption the upper prickle cells are completely normal and pass into a normal granular and horny layer, they are, towards the centre, swollen, less deeply stained, come close together without definite prickles, and are at the same time flattened from above. The granular layer above disappears and the flattened œdematous prickle cells pass directly into nucleated, flat horny cells, although certainly by appropriate staining the margin between the cornified and uncornified cells may still be clearly distinguished. We have then to do, as in eczema and psoriasis, with a true parakeratosis, accompanied by loss of the granular layer, only with the difference, that the renewal of the epithelium by new formed prickle cells is less,

and therefore the upper prickle layer, which is being converted into a scale, sinks in somewhat (relatively to the periphery), and adheres more firmly to its foundation.

The implication of the cutis, and especially of the papillary body, at this time is greater than one could believe from the clinical appearances. Not only are the blood vessels of the superficial net markedly dilated, as are the lymph spaces in the neighbourhood of the blood vessels and in the papillary body, but there exists, even in the small eruptions, an abundance of new connective tissue cells. The layer of new formed, mostly multi-nuclear perithelium which accompanies all the blood vessels in the centre, is much broader and more cellular than in the eczematous or psoriatic eruptions of the same age and size. The cells all maintain their spindle form, and only a few leucocytes escape from the vessels. It is thus a purely serous, hyperplastic inflammation of the upper half of the cutis in the centre, and of the papillary body at the periphery of the eruption.

The second stage of the eruption, in which the papular character is definitely present, is shown by an increase of all the symptoms described ; acanthosis and parakeratosis of the epithelium, inflammatory œdema and cellular formation in the cutis. The changes in both layers together lead to the papular elevation. The epithelial growth and extension of the ridge system increase, but retain the same irregular type of distribution over the surface. The inter-epithelial œdema of the lower prickle layer leads here and there to the formation of net-formed, branched, wide canals between the still preserved epithelial cells, which now contain rather more leucocytes. Peculiar and—for pityriasis rosea —rather more characteristic changes are shown in the upper prickle layer, which, up to now, has presented the appearance of parenchymatous œdema, with dilatation of the lymph spaces. This coherent cell layer gives way at certain places to the pressure of the lymph stream, and there are thus formed sub-corneal pressure vesicles of very irregular form, which are not macroscopically visible. These pass here and there directly into the wide canal system of the under prickle layer ; they contain mostly only serous exudation and loose epithelial cells, rarely any considerable number of leucocytes. The whole process gives the impression of the violent escape of serous exudation into a very resistant prickle layer with no tendency to colliquation ; those lymph spaces in the under prickle layer, which have already yielded, are still more dilated, but in the upper prickle layer, where they are in general closed by parenchymatous œdema, the stream of fluid escapes only at certain places, and leads to rupture of the connecting threads, and not, as in the vesicles of eczema, to globular rounding and smooth, large cavities. These very small, irregularly

arranged vesicles are, in the centre, directly adjacent to the thicker scales, which consist of nucleated horny cells, are almost free from leucocytes, and scale on the surface.

The inflammatory new formation of cells in the cutis has now made further progress, and converted almost the whole papillary body into a continuous net of spindle cells, with stellate connecting processes. This affection might be used for the study of inflammatory swelling, hypertrophy and proliferation of the spindle cells of the cutis, so pure, and in such amount do these appear. From the broad cell mantle of the blood vessels, the new formation of cells extends outwards to the middle of the cutis, and along the vessels still further outwards, up to the epithelium. Only the sub-epithelial marginal area is relatively free from cells, a circumstance which also points to the slight share of leucocytic emigration. Only where, under the horny layer, small vesicles are present, do more leucocytes tend to leave the vessels, and thus to make the under margin of the epithelium less sharp. Most of the spindle cells have two, three, or more nuclei, and one also sees in them a considerable number of mitoses. But a certain want of relation between the mitosis of the epithelium and the cutis is here, as in many inflammatory dermatoses, striking. For in the enormous mass of nuclei which, in the latter, have developed in a very short time, and are not derived from leucocytes, there must be, compared with the epithelium, more mitoses than one can recognise. A few plasma cells are also found at this stage of the eruption, but these do not stain so deeply, are not so granular and almost cubical in shape, as in the granulomata, but in their loose arrangement and irregular form rather resemble the spindle type. Mast cells are not specially numerous, and are mostly round.

If we review these appearances, the most striking is the resemblance of the process to that of papular, and especially of flat papular, seborrhœic eczema ; the combination of epithelial growth, parakeratosis and inflammatory cell growth in the cutis. But when one compares fresh, acutely developed papules from both affections, there are ample characteristic distinctions for pityriasis rosea ; in the cutis, the increased œdema, the much more rapid multiplication of the spindle cells, especially those of stellate type ; in the epithelium, the irregular distribution of the epithelial growth, the greater resistance of the prickle cells, and the acutely developed parenchymatous œdema of the upper prickle layer, by which the formation of vesicles is limited, and the crusts which develope come to lie deeper, the relatively slight leucocytosis, the absence of fibrin, and, therefore, the absence of thick fibrinous crusts, and, finally, the absence of morococci.

The scales removed from the spots of pityriasis rosea are distin-

guished, when stained, by the absence of any readily recognisable organism, and in this relation are something like psoriasis scales.

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Pityriasis Rubra, Hebra.

A stealthily appearing, very chronic, usually fatal disease, which is accompanied by constant fine scaling of the dark reddened skin, and extends diffusely over the whole body. It is chiefly characterised, negatively, by the absence of distinct infiltration of the cutis, of papules, vesicles and fissures, of weeping, and of much itching. The hairs fall out, the nails usually remain intact. The general condition is only affected just before the end; the only subjective symptom is a feeling of cold. There gradually developes pigmentation and atrophy of the whole skin, with much tension, which leads to flexion of the joints and bed sores. The lymph glands which can be felt, are mostly swollen. Many of the affected patients become tubercular (Jadassohn).

Under pityriasis rubra, I include only the severe cases corresponding completely, or at least in the main points, to the above description, which, on the one hand, can be distinctly separated from the final exfoliative stage of eczema (psoriasis), and, on the other hand, from the Dermatitis exfoliativa of Wilson and Brocq, and I lay value, following Hebra's first description, on the fine, doughy quality of the scales, and then on the unity and severity of the progress. Not all the cases which are histologically examined under the name *pityriasis rubra*, Hebra, come under this narrow definition, and must, therefore, be here excluded.

H. v. Hebra first had the opportunity of examining the skin of two tubercular patients who died of pityriasis rubra. In one recent case there were, except for a cellular infiltration of the cutis, especially round the vessels and sweat glands, no striking changes; in particular the epidermis and its appendages were intact. On the contrary, in a very long (at least thirty years) standing case the skin had completely lost its normal structure. A rich growth of cells filled all the layers of the skin down to the subcutaneous tissue, but was most developed directly under the epidermis, which was reduced to a thin prickle layer, closely permeated by infiltration cells (leucocytes ?). The ridge-net, and with it the papillary body, had disappeared, and the infiltrated epidermis sat directly on a thin layer of much infiltrated cutis. Then followed a layer of cutis, three times as broad, in which the cellular infiltration was less, but in which a rich net of elastic fibres and yellowish-brown granular pigment appeared. In many sections the pigment reached up to the epidermis. No sweat glands were found, and in all the sections only one sebaceous gland and one hair.

At the time of his publication we did not know of the richness of the normal skin in elastic fibres, and, therefore, the suggestion of a new production, elastin, in a skin otherwise atrophic, must be taken with caution.

Cahn, who also had a highly developed case, with tense skin, in a child, confirmed the cellular infiltration, but he found no atrophy of the ridge system, of the papillæ, or of the follicles and coils. The horny layer was widened, and contained many cells with stained nuclei.

Elsenberg's observations are properly and solely related to a moderate cellular infiltration of the whole cutis, which, however, according to his statement, reached its highest development in isolated small areas around the follicles, especially between the arrector and the hair. The epithelium Elsenberg found normal, except for a few immigrated leucocytes and a thickened horny layer. An abnormal size of the coils, described by him, is the normal condition in that part of the skin (Axillary cavity).

The examination carried out in my laboratory by Tommasoli was on pieces of the skin of an old man, who died with appearances which were very like pityriasis rubra, but which had developed under my observation from a universal seborrhœic eczema. I have referred to it under the exfoliative stage of seborrhœic eczema.

Petrini and Babes in their case certainly described complicated changes in the tissues. They found, in a piece of skin from the leg, the horny layer beset with nuclei, transformed into lamellæ; the granular layer thickened, the prickle layer not much altered. The papillæ showed a strikingly thin and sclerotic quality, and from the papillary vessels, downwards through the whole skin, the walls of all the vessels were thickened, homogeneous, and very refractile, surrounded by a quantity of shining and fatty granules, and, owing to their rigidity, did not present their normal twisting. Then the connective tissue fibres were thickened and sclerotic; the elastic fibres and muscles were present in abundance. In a few sections there were found at the apex of the papillæ "embryonic" cells without stainable nuclei, while the papillary edge, next the epidermis, was converted into a uniform sclerotic band.

A piece, excised from the arm four months later, showed, in addition to the appearances described, a parakeratosis of the epidermis, the horny cells nucleated, the granular layer feebly developed, and the prickle layer thickened and permeated by branched cells, which, after treatment with gold, were seen to be connected by their processes. The authors here described the net of "gilded" cells of the papillæ, as it may be seen in almost all inflammations with immigration of leucocytes.

In the vessels there were sometimes coagulated, red-stained, or hyalin, yellow-stained masses (Picro-carmine). The elastic fibres and muscles were everywhere abundant; whether they were new formed, is not directly stated. The hair follicles were atrophic, dilated at their mouths like filters, the sebaceous glands had disappeared, and in their place were found lobules of fat. The coil glands contained granulated cells, and their ducts hyalin masses.

Summing up their results, Petrini and Babes speak of a hypertrophy of the collagenous substance and an increase of the elastin and of the smooth muscles, though this does not appear to be sufficiently supported by comparison with the appearances of normal skin from the same region. The replacement of the sebaceous gland by a lobule of fat, assumed by them, involves an unnecessary assumption, for extending lobules of fat are very common, that drawn by them (in Fig. 5) occupies its normal position near a sweat gland. The most important observations are, in my view, those concerning the degeneration of the collagenous substance of the papillæ, of the vessel walls, and the recognition of thrombi in the vessels.

Jadassohn found in both his cases a slight round-cell infiltration, which was most marked in the papillary body, and in the sub-papillary stratum, as well as groups of round cells, but not in any special follicular areated arrangement, like Elsenberg. The nuclei of the fixed connective cells are increased; the mast cells are very numerous in the papillary body and around the coils. The cutis is rich in pigmented cells, while the germinal layer is strikingly poor in pigment. Very few leucocytes are found in the epithelium, bnt there are numerous mitoses. In the older case the prickle layer was thinned. Jadassohn found the same changes in the horny layer as Petrini and Babes, viz., marked parakeratosis with diminution of the keratohyalin, retention, nucleation and splitting of the horny layer into lamellæ. But he could not find, as these others did, any definite degeneration in the connective tissue and the blood vessels, nor did he find the elastic tissue abnormally rich.

I have no observations of my own on the pure form of Hebra's Pityriasis rubra. Those quoted put it beyond question that we have to do with an inflammatory process, reaching its acme at the surface of the skin, and tending to abnormal cornification; consequently with a dry catarrh of the skin.

But the individual peculiarities are histologically but little explained. Only the constantly increasing darkening of the skin is explained by the wide-spread pigmentation of the cutis. Two clinical symptoms especially require histological explanation; the striking persistent hyperæmia, and the later appearing atrophy and tension of

the skin. It is clear that observations such as the obliteration of the superficial vessels by sclerosis of their walls, however important they may be in relation to the later atrophy, hardly correspond to the hyperæmic character of the affection. And in relation to the changes in the collagenous, elastic and muscular tissues, there are directly contradictory statements. H. v. Hebra alone appears to have had, in one case, the final atrophic stage of pityriasis before him; but the development up to this stage is quite obscure. The nature of the cellular infiltration requires investigation with newer and better methods.

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Dermatitis exfoliativa (Wilson-Brocq).

A disease, with discrete, red, itching spots, which run together and extend, in the course of a few days, over the whole body; there are no vesicles or papules, and from the commencement it is accompanied by constant, severe, coarse, mostly lamellar scaling, which is not greasy. There very soon follows loss of the hair, and a disease of the nails which leads to their loss. The general condition is almost always disturbed by various complications of the internal organs, fever is always present, and there is much complaint of itching and burning. The disease runs a course lasting many months, but usually ends in complete recovery. Compared with the exfoliative stage of other parakeratoses (Eczema seborr., Psoriasis) the absolute universality of the eruption (there is not a single healthy spot on the whole body), the rapid extension and the benignity, are of importance in the differential diagnosis.

Girode, in his case, found the horny layer of varying thickness, the supra-papillary prickle layer excessively thinned, while the inter-papillary ridges were hypertrophic and the papillæ correspondingly elongated. The keratohyalin in the granular layer was somewhat diminished.

The collagenous bundles of the cutis were thickened, and closely surrounded by some rows of "embryonic" cells. The hair follicles were shortened, and presented irregular excavations and constrictions, the hairs were thin, laid and retained in the cystic dilatations. The sebaceous glands were excessively atrophic or had completely dis-

appeared. The coil glands had increased in volume, their lumen being filled with swollen epithelium; their ducts were prominent from their intra-cutaneous twisting, and sometimes ran, for a short distance, parallel to the surface. The capillaries, especially of the papillæ, were filled with blood and usually surrounded by a mantle of "embryonic" cells, as were the lymph vessels.

Vidal and Leloir, the former of whom had already treated of the pathological anatomy of the disease, recently summed up their results in their Atlas, to this effect. While the epithelial ridges are changed in form but not exactly hypertrophic, the supra-papillary prickle layer is always thinned; the prickle cells are flattened horizontally, the granular layer is absent, the basal horny layer retains its nuclei, and the upper layers of the horny layer are beset with unstained nuclear remains, and desquamate irregularly. The cutis, excised from the living, is succulent—in contrast to Pityriasis rubra,—and, in the papillary part and the sub-papillary zone, considerably infiltrated by round cells, among which only a few spindle cells are still visible. Underneath the sub-papillary vascular net the cellular infiltration is much more sparing, and only accompanies the vessels themselves. The collagenous bundles are—in contrast to the terminal, exfoliative, malignant stage of the other catarrhs (Eczema, Psoriasis)—completely normal. The blood vessels are distinctly dilated, as are occasionally the lymph spaces. The hypoderm is always normal. The peripheral cutaneous nerves, which were examined in one case, were healthy—in contrast to their condition in Quinquaud's "Dermite aiguë grave primitive."

The observations of Buchanan Baxter partly correspond with those of the French authors, but relate to material, whose origin from pure cases of Wilson's disease is by no means certain. The affection of Quinquaud is also a different one.

The statements of the French authors present a pretty definite picture of the disease, so that the anatomy of this affection is better known than that of Pityriasis rubra Hebra, which is often confused with it. It is to be hoped that the differential diagnosis of these two affections, in their histological relation, will be further and thoroughly investigated.

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Dermatitis scarlatiniformis recidivans.

(Dermatitis scarlatiniformis generalisata recidivans Vidal-Leloir, Dermatitis exfoliativa acuta benigna Brocq, Erythema desquamativum scarlatiniforme recidivans Féréol, Besnier.)

This catarrh of the skin, which externally, in its acute course and the scarlatinal redness, resembles true scarlatina, and is frequently mistaken for it, is regarded by Brocq as an acute variety of Dermatitis exfoliativa generalista (subacuta) Wilson-Brocq, to which it, even of the scaling Erythrodermata, stands nearest. Since in the adjective scarlatiniform both the scaling and the generalization are expressed, I prefer the above shorter title.

After febrile prodromata of two or three days' duration, there appear red spots, which rapidly run together to a universal redness. This is dotted like scarlatina, affects also the mucous membrane of the mouth; but there is no strawberry tongue. The trunk, especially around the flexor sides of the large joints, is first affected, then the neck, face, and extremities. Three or four days later there commences, with the decrease of the fever, a general, chiefly lamellar, very free scaling, with which—in about three weeks—the disease definitely terminates. It is almost characteristic of the affection, that it rarely terminates in a crisis; there usually follow, at long intervals, several, of which the later are usually mildest.

From scarlatina this affection is distinguished by the absence of the well-known extradermal symptoms, the absence of contagiousness, the commencement of the redness on the trunk, its long duration, and the early commencement and the severity of the scaling. From Hardy's "Scarlatiniform Erythema," it is distinguished by the longer duration, the greater severity of all the symptoms, and the coarse scaling. From certain drug eruptions the affection is often only distinguished with great difficulty.

Suchard and Siredey found, on examining the skin, the blood vessels of the papillary body dilated; the latter infiltrated with "embryonic" cells, the ridge net of the epidermis thickened, the papillæ correspondingly elongated, the granular layer absent, and the horny layer nucleated where scaly formation existed, consequently the type of an acute, dry catarrh of the skin. When Petrini, on the contrary, found a broad layer of granular cells, and thought it necessary to constitute a different condition to psoriasis and to eczema, he was wrong. The two observations are not contradictory, but confirm one another (see on this, the chapter Psoriasis). Petrini had excised a later stage (of scaling), which, under the new horny layer, would present a broader granular layer. His drawings distinctly show the old leafy scale and the young horny layer of basal type.

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Darier's Dermatosis.

(Psorospermosis follicularis vegetans.)

An exceptionally chronic dermatosis, specially localised on the trunk, on the most sweating and greasy parts, the anterior and posterior sweat channels, the neck, the axillæ, the inguinal region, in lesser degree on the face and extremities, especially the backs of the hands. The elementary lesions consist of dirty yellow-gray, or brown crusts, sometimes elevated like horns, and difficult to remove, though the removal does not cause bleeding. One removes with it a whitish yellow, soft process, which sometimes, but not always, corresponds to a dilated follicle. The lesions run together, on the predilection areas, into dried, brown, greasy crusts, which can only be removed by force, and on their removal leave a red, moist surface, covered with depressions. In very long-standing cases (Darier's second case : inguinal region) the elements assumed the character of larger nodes, which were covered with crater-like openings, and which ran together to form red, moist tumours, covered with stinking secretion. The nails always share in the process, with proliferation of the sub-ungual horny layer.

Darier has the great credit of having introduced this peculiar disease, both clinically and histologically, to science. But on his explanations of the histological appearances, which have been mostly confirmed by later authors, there arose at once a vigorous debate, for, as the title of the disease indicates, he regards certain constituent of the lesions as psorosperms.

The most important of Darier's histological observations are the following :—It is a superficial inflammation which attacks chiefly the upper part of the follicle, and, extending from here, also the interfollicular part of the skin, while the lower section of the follicle remains intact. The mouth of the follicle is dilated like a filter, and filled with horny cells and peculiar bodies. These filters are surrounded by a specially well-developed granular layer, and by a prickle layer, which extends irregularly into the cutis, whose cells have lost their regular arrangement, and are frequently separated, so that regular fissures and spaces appear between them. In the prickle and granular layer there lie peculiar " round bodies," about the size of the epithelial cells, with granular protoplasm, well-defined nuclei, and a double contoured membrane. These bodies lie in dilatations, from which they readily fall out ; the dilatations appear to be in the prickle cells. Their tinctorial relations are not alike, and Darier was unable to find any specific stain for them. As they rise in the horny layer the bodies change, their size becoming less, their nuclei less distinct and less stained, and the membrane completely disappears. Transformed in this way into round or oval, very refractile " granules," they form the main constituent of the horny plug, which lies in the follicles.

These elements are found in the epidermis and in the crusts between the follicles. Darier made squash preparations from the

cornified crusts and plugs by macerating them with caustic potash (40%), ammonia (10%), or bichromate of ammonia (2%); the uncornified masses from beneath, after removing the crusts, showed at once, or on examination in iodine serum, the "round bodies," and they are often observed free and often enclosed in epithelial cells. The granules of the horny plugs, on the contrary, were never found within the cells.

The hypertrophy into larger nodes, in the inguinal region, developes by a moderate epithelial growth, in the manner of a "papilloma," and in it "round bodies" are also found.

From the absence of connecting threads, from the refractile membrane, the nature of the nucleus, and the intra-cellular situation, Darier concludes that these "round bodies" are not degenerated epithelium; Malassez and Balbiani have further recognised the resemblance of the "round bodies" to certain coccidia. Therefore Darier ascribes the other appearances of the disease—the keratosis, acanthosis, and the superficial inflammation, to the penetration of the "round bodies"—that is, in his view, to the infection with psorosperms.

Buzzi, from squash preparations, describes Darier's granules as greenish, shining bodies, quarter or half the size of the horny cells, containing, in their interiors, rough, nucleoid bodies, often surrounded by a small, light halo or fine granules, or containing irregularly distributed, bright spots; they are found in excavations of the horny cells lying free, singly, or in groups. Darier's "round bodies" are twice as large as the "granules," are surrounded by a distinct hyalin, doubly-contoured membrane, and filled with a very fine granular substance, which is separated from the central shining nucleus by a light halo. They are intra-cellular or extra-cellular; the latter are the transitional stages to the "granules." The intra-cellular structures sometimes lie in pairs in an epithelial cell. The epithelial cells are otherwise unaltered.

In sections, Buzzi found that the horny plugs were not specially localised in the mouths of the follicles, but were most frequent at the seat of the sweat pores, which were closed by the plug and cystically dilated. In these cysts, which were seated at the level of the basal horny layer, there was a granular substance, and, in addition to broken-down cells, coccidia-like structures. Buzzi, like Darier, found the glands and follicles otherwise normal, and in the cutis an inflammatory, cellular infiltration, especially in the papillary body, diminishing outwards along the vessels, and frequently enclosing pigment. The epithelium immediately around the eruption was deeply pigmented.

Buzzi regards as characteristic of Darier's disease, the spaces constantly present in the under part of the prickle layer, underneath the horny plug, to which Boeck first drew attention. While the papillæ

at the side of the plug are lengthened and made smaller, some of them possess underneath a short rounded form, and are only covered by a single layer of prickle cells, while others stretch high up into the prickle layer, and are connected with it. Between the papillæ of the first variety and the prickle layer lying above them, there are found these very irregular spaces and cavities, which Buzzi regards as a sort of abortive inflammatory vesicle, whose extension is prevented by the pressure of the horny plug seated above it. In the neighbourhood of the spaces, some of the prickle cells, which up to now have been

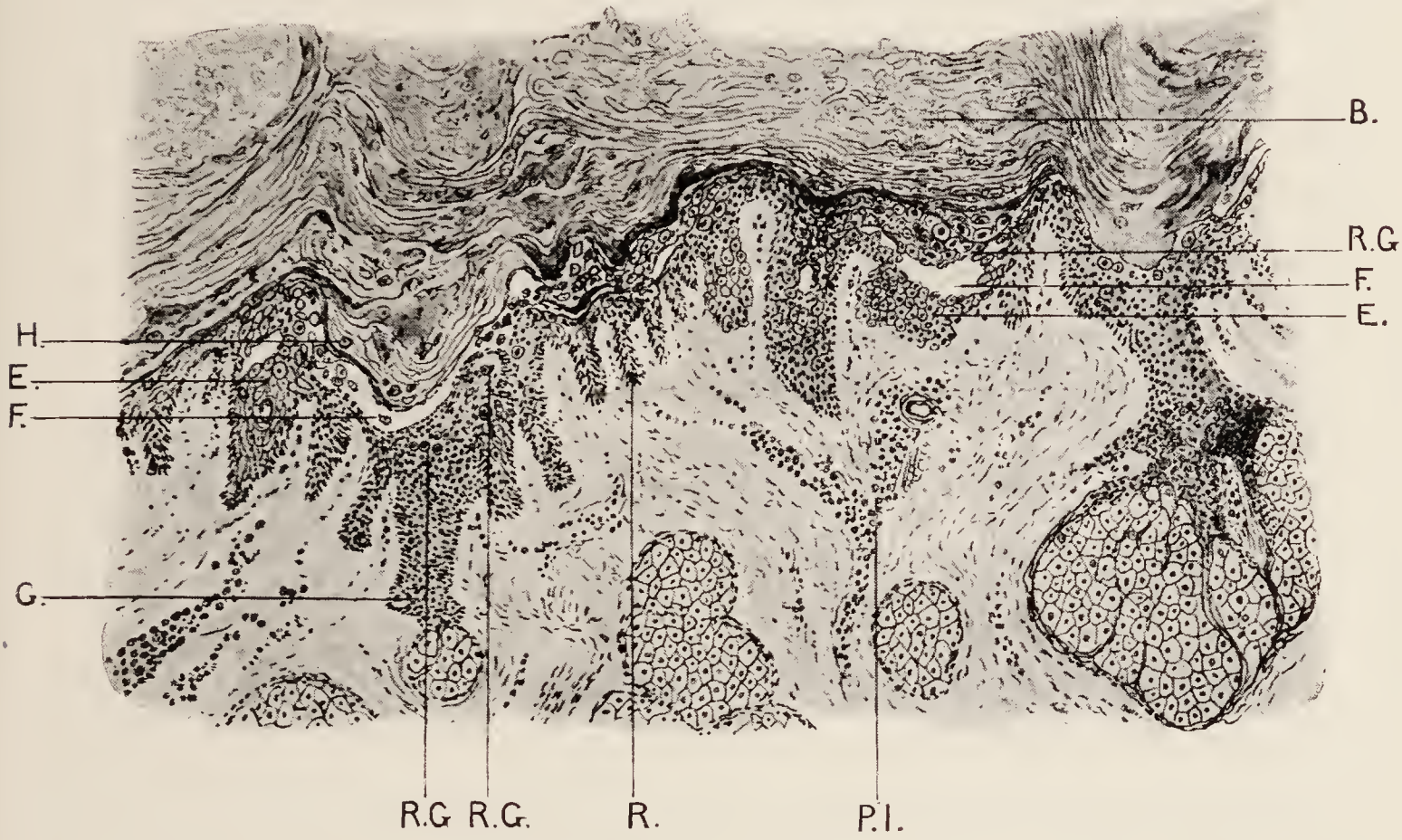

FIG. 10.—Darier's Disease.

R.G. Darier's round bodies, partially hyalin prickle cells.
E. Swelling of the prickle cells.
F. Fissuring in the prickle layer in the neighbourhood of the hyalin degeneration.
H. Enormously thickened horny layer, containing a few hyalin clumps, Darier's Granules.
B. Collection of bottle bacilli in the loose upper parts of the thickened horny layer.
R. Actively proliferating epithelial ridges.
P.I. Infiltration of the cutis, consisting mainly of plasma cells.
G. Lateral section of a proliferation of the prickle layer of the hair follicle.

normal, are loosened, lose their prickles, are disarranged and detached from all connection, and fall into the spaces. Their nuclei lose their staining capacity, and their protoplasm becomes shiny and hyalin. Buzzi regards these epithelial flakes as the predecessors of Darier's "grains." In addition to them, a few leucocytes are found in the spaces.

The "round bodies" of Darier are formed in very large epithelial cells (host cells), three to six times their normal size, whose nuclei and prickles are always absent, and which are distinguished by a peculiar

shimmer. The surrounding epithelial cells are arranged, like the scales of an onion, around those cells, which are mostly filled with very large coccidia-like bodies. In the latter there are found, as Darier noted, granules, with the staining capacity of kerato-hyalin, although the surrounding prickle cells contain no kerato-hyalin. The round bodies are consequently undergoing premature cornification. Thus, inside the granular layer, which, at the side of the horny plug, is well developed, under it less so, irregular or altogether absent, they are very like the granular cells themselves, and are only distinguished by the refractile capsule.

In the basal horny layer the elëidin is, compared to the kerato-hyalin, sometimes collected in quantity, sometimes absent. The "round bodies" are here still more numerous than in the granular layer, and lie peripherally, inside the cell mantle of larger horny cells. The "granules" have run together into globes; extra-cellular. In the horny plug itself, and also in sections, may be found cells with coccidia-like contents. "Granules" are sometimes piled up alternately with collections of (leucocytic ?) nuclei, especially on those places which lie over much degenerated hyalin parts of the prickle layer.

Buzzi, whose cultivation experiments were, like Darier's, negative, regards the extra-cellular "granules" as degenerated prickle cells, the intra-cellular "round bodies" as the result of endogenous cell formation; both these structures have, according to him, nothing to do with coccidia.

Since the observations of all authors in the main agree, so far as concerns the facts, I have placed first the two most thorough descriptions, which, at the same time, differ widely in their explanations, and will now only add a few details from certain others, in order to complete the picture. Bowen, who examined White's case, could not convince himself of the coccidial nature of the structures, and drew attention to their containing kerato-hyalin, as a sign of their epithelial origin. Lustgarten, on the contrary, agreed with Darier's explanations, but laid stress on the extra-follicular development of a great part of the horny plug, in which all later investigators agree with him. Boeck again, to whom we owe a very careful investigation of several cases, very decidedly regards the "round bodies" as prematurely cornified prickle cells, and the "granules" as probably degenerated prickle cells; but recognises only differences of degree between them. Thus Boeck does not accept the view of all other investigators, that *only* extra-cellular structures are present, that the apparent encysting is confused, partly with the "fitting-in" to the excavations of the epithelia, partly with the shell-like flattening of neighbouring epithelia. According to him, the lighter space around the "round body" does not correspond to the protoplasm of a host cell (Darier, Buzzi), but represents the

thick cornified membrane of the same epithelial cell, whose nucleus represents the nucleus of the questionable structures (Darier's coccidia; Buzzi's endogenous epithelial cells). According to Boeck, then, the "round body," and the space around it, is a unity; according to other authors a complex of two elements. The lacuna formation in the depths of the proliferating prickle layer, Boeck does not regard, like Buzzi, as an abortive vesicle formation, but as a separation, a result of the degeneration of the epithelium, and especially of the loss of its prickles,* for it is present in the peripheral parts of the very smallest papules, where the epithelium as a whole shows no distinct changes.

Through the kindness of the authors, I obtained sections from three of the cases described (Darier, Lustgarten, and Buzzi-Miethke), and had therefore ample opportunity of testing and confirming the correctness of most of the statements. In regard to the significance of the structures in question, especially of the "round bodies," I agree, in the main, with Boeck. I think it is beyond doubt, that these represent hyalin degenerated epithelia. All the apparent peculiarities and the specific nature of these structures are removed, if they are compared with the hyalin epithelia of other dermatoses. In certain carcinomata, one finds, sometimes exactly the same, sometimes still more striking results of the hyalin degeneration of the epithelium (cysts, double cysts), and in Lichen, in Ulerythema centrifugum, in Pityriasis rubra, structures, which exactly resemble the small "granules" (see chapters alluded to). As in the carcinomata, I regard the external, solid, broad, glassy ring as hyalin swollen ectoplasm, the inner, small, doubly-contoured one as endoplasm, which in some epithelial cells is only compressed, in others, has also undergone hyalin degeneration (Acidophilic). Between the endoplasm and the, at first, still preserved nuclei, the keratohyalin naturally collects, until it disappears in the higher, cornified layers. The hyalin degeneration of the ectoplasm leads to the disappearance of the prickles, and to the lateral separation of the epithelial cells, and thus to the formation of fissures, which play so great a rôle in Darier's dermatosis. In this tendency to individualisation of the hyalin epithelia, lies the reason, that the tail-like processes (hyalin degenerated connecting bridges), which distinguish this degeneration in carcinomatous epithelium, are here absent.

Only here and there is the connection between two neighbouring epithelial cells hyalin, and then the ring which developes surrounds two of Darier's bodies; *i.e.* two nuclei, which are each surrounded by shells of their endoplasm. But if the hyalin degeneration attacks

* Auspitz's name, acantholytic formation of vesicles, would here be quite suitable.

quite young epithelia, in which no distinction into ecto- and endoplasm is present, there simply develope, small hyalin clumps, with more or less well-preserved nuclei;* such is, so far as I can see, the development of Darier's granules.

Nor do I believe that the "round bodies" are partly converted, in the horny layer, into granules; though I have noted transitions between the two forms. The hyalin degeneration attacks both younger and older prickle cells, which may pass as gradually into one another as the results of their degeneration. As usual, the hyalin degeneration attacks the nuclei proportionately late; indeed, in a few "round bodies" of the deeper prickle layer, there may be found two to four epithelial nuclei, so that these bladder-like cells, filled with nuclei, have a certain resemblance to another kind of cell, also filled with nuclei, but softer and acutely developed; the bladder-like cell of ballooning degeneration (Zoster, Varicella). Consequently I believe with Boeck that the presence of endo-epithelial structures can be excluded; Darier's bodies all develope from single, or it may be from two neighbouring epithelial cells.

The cellular infiltration of the cutis is, as a whole, slight; I could only occasionally find areas of plasma cells. The number of leucocytes is strikingly small.

Krösing has recently described from Eichhoff's klinik a case of Darier's dermatosis, preparations of which he sent me. I have not included this case in the above discussion, for both the clinical and histological appearances present marked deviations from the true type of Darier's dermatosis, and the inclusion of this case would only lead to confusion. The inflammatory infiltration was very marked, and the formation of fissures in the epithelium minimal—or absent. Hyalin degeneration of the epithelium was indeed present, but by no means in the striking degree, nor accompanied by the same conditions as in the true cases. The sections resemble rather some lichenoid disease than Darier's; from the corresponding appearances of the three true cases I have seen, I think I can definitely state that. In the future it will be wiser not to regard all parakeratoses, accompanied by hyalin degeneration of the epithelium, on that ground, as Darier's dermatosis.

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Keratosis follicularis contagiosa (Brooke).

An abnormal cornification, spreading contagiously in children, and appearing sporadically in adults, which appears especially on the extensor surfaces of the extremities, the neck, and trunk, but also on the face, the flexor sides, and the nates, and, slowly healing, extends gradually from one region to another. On the affected parts there is first visible a general thickening of the horny layer, shown by the coarsening of the epidermic furrows. Inside these polygonal areas there appear several black points, of which usually one developes, at the expense of the others, into a dark spike reaching out of the follicle. At the same time the affected region of the skin gets a dirty yellow colour. The comedo-like, horny plugs swell up into non-inflammatory, brownish, large papules, from whose apices the horny spikes project, straight or bent. The height of the spikes varies according to the region of the skin, and is not dependent on the size of the papules ; they are longest on the neck and posterior axillary furrow, while on the arms and legs the pretty large papules only have comedo-like plugs. This absolutely dry, non-fatty affection, after a short time, heals spontaneously, or under simple treatment.

To this affection certainly belongs Morrow's case (Keratosis follicularis) in a young sailor, but not White's case (Keratosis s. Ichthyosis follicularis ; Journ. of Cut., 1889, No. 6). Probably also the more localised forms of so-called acne sebacée corné (Hardy) of the face, neck, back, and buttocks come under it, although the histological description by Leloir and Vidal does not completely correspond with that of Brooke, which I can confirm from the preparations he kindly sent me.

As Brooke states, the hyperkeratosis is a general one, not limited to the follicles alone. It is always extended superficially in their neighbourhood, and extends a certain distance into the sweat pores, as well as into the follicles, without leading there to the formation of horny masses.

The pathological changes in the follicles are more multiform than the clinical appearance suggests. Two main groups of changes may be distinguished—(1) simple appearances of retention ; (2) formation of horny plugs at the seat of the follicles. The appearances of retention develope from the closure of the follicle with horny layer, and consist in the formation of comedo-like cysts, or in deformities of the hair and of the whole follicle. Where horny cysts are developed, the hyperkeratosis of the surface epithelium is extended to the prickle layer of the follicle. Then the upper part of the follicle becomes more and more filled with vertically arranged horny masses, and is converted into an oval, later a globular, horny body, which is sur-

rounded by a small border of prickle cells. From the comedones of acne these horny cysts are at once distinguished by the fact that, from the commencement, they are surrounded at the base by horny lamellæ, and also by the absence of sebaceous cells. On the contrary, they also enclose a hair; for the inclusion of several hairs the duration of this sub-acute affection is evidently too short. The sebaceous glands atrophy during the process, or may be found, well preserved, at the base of the horny cysts, along with the remainder of the hair follicle. Instead of affecting the upper part alone, the hyperkeratosis and cystic transformation may attack the whole follicle. Then the remains of the hair follicle and the sebaceous gland are completely taken up into the cyst wall, and what was a follicle is now represented by a large horny pearl, lying under the surface.

In other cases the hyperkeratosis is limited to the mouth of the follicle, and, by retention of the hair and spiral twisting, induces, first in it, and then in the whole follicle, appearances resembling those of ichthyosis and keratosis pilaris. Either the hair describes a spirally twisting course in the softened prickle layer of the hair follicle, or the follicle follows, in lesser spiral windings, the course of the hair, so that ordinary perpendicular sections only show a series of segments, in every one of which the hair has a different direction. The prickle layer of the hair follicle is, at the same time, often somewhat thickened. If the hyperkeratosis is very superficial, the hair keeps its straight direction to the mouth of the follicle, and here first describes a series of flat, large, spiral twists, resembling the appearances in hyperkeratosis supra-follicularis.

The changes just described have a purely microscopic interest, for they are not visible on the surface. Their presence only proves that these rapidly extending hyperkeratoses can induce all the follicular changes, from those of Acne to the so-called Lichen pilaris, which the more chronic keratoses present singly, in purer development.

Of more interest to us, are those results of hyperkeratosis, which are clinically evident, and give the affection its particular stamp—the formation of horny spikes. In these cases the follicle is not closed; the hyperkeratosis so early attacks the epithelium of the follicle, and produces so energetic a horny growth, that it cannot be held back by the less thickened horny layer of the surface. There also develope somewhat different forms, according as the hyperkeratosis attacks only the upper part of the follicle, or the whole of it, down to its lower end. In the latter, simpler cases, new horny lamellæ are constantly being interposed between the hair and the prickle layer of the follicle; this is more marked high up. The follicle is dilated, like a filter, running to a point at its lower end, while its mouth is widely open.

The hair still runs in the central axis, and is surrounded, concentrically, by a number of small horny plugs, running to a point below. Consequently, it gradually advances above the surface of the skin, and forms a short, blunt, horny spike. The very lowest end of the follicle and sebaceous gland may still be preserved, or they may share in the process.

More frequent and more characteristic of Brooke's affection is the limitation of the hyperkeratosis to the upper open end of the follicle, which then becomes cylindrical or goblet-shaped, sometimes with a short, under portion of the follicle adherent. But usually the lateral extension of the upper part of the follicle is so great that the whole under part is taken up into it. We then have a horny body, widely open above and semi-spherically limited below, and only extending a short distance into the cutis, which would rather suggest a simple cornified epithelial ridge than a cornified follicle, were not the hair belonging to it still visible. Since the flat shell of prickle cells, surrounding this horny body, continues rapidly to produce cornified masses, a horny body is gradually elevated above the level of the skin, apparently consisting of a series of cups or goblets, inside each other. The uppermost horny goblets are the oldest and smallest, the undermost are the youngest and largest, for the matrix constantly extends somewhat in breadth. Thus the ascending horny columns acquire a pointed, spiky form, and the long thin horny spikes develope. Only rarely are they quite isolated, microscopically; usually they are surrounded by a small horny depression, which is not macroscopically visible, and almost invariably there is found beside them, one, or a pair of well-preserved follicles, which show the above appearances of retention.

The explanation of the clinical condition is quite evident from these observations; at the commencement we see only black points, the closed mouths of a group of two or three follicles forming a hair circle. Then the hyperkeratosis in one follicle becomes so great that the covering gives way, and a broad, deep-rooted, or shorter horny tap, or a smaller, superficially sunken, but all the longer, horny spike is produced. Retention then induces, on the neighbouring follicles, the deformities already described.

The horny substance itself is very homogeneous, and mostly a-nuclear, especially where, by a broad granular layer, it is separated from the prickle layer. At the base of the horny spikes the keratohyalin frequently diminishes under the pressure of the horny body, and consequently the nuclei are preserved. But there is also in many places a welding of the horny layer, and nuclear remains are again evident on staining. Hyalin degeneration and coccidia are never found, nor is there any resemblance to Darier's disease.

The cutis shows in the neighbourhood of the affected follicles, and elsewhere in the papillary body, signs of a slight infiltration; many vessels are surrounded by numerous new cells, and in the neighbourhood of the follicle there are here and there evident, areas of new formed cells; the elastic fibres have disappeared. In addition, the papillary and sub-papillary vessels are almost everywhere dilated.

In assuming a slight, superficial, but distinct inflammation in this disease, neither more nor less than in many dry catarrhs of the skin, I do not altogether agree with Brooke. Were this not present, the affection would have to be ranked with the keratomata. In spite of the affection of the follicle, the disease in its whole character belongs to the superficial inflammations, and therefore I place it, not with Acne, but with Ichthyosis and Keratosis pilaris.

In addition to this case, I had the opportunity of examining a more localised Keratosis follicularis, taken from the corpse of an adult. I found exactly the same changes, though in lesser degree, as in the case just described. There was general parakeratosis, slight acanthosis of the surface of the epithelium of the affected parts, and, consequently, appearances of retention in the follicles, and formation of follicular horny plugs. The latter had the type of thick, short taps, formed of horny scales, while thin spikes were absent. Morrow's case, which was examined by Robinson, appears to have resembled these cases.

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Parakeratosis scutularis.

A very rare affection, only once observed, characterised by an abnormality of cornification, affecting the body in areas, and combined with superficial appearances of inflammation. Inside the yellowish-brown, on the leg, livid red-coloured spots, the size of a shilling to half-a-crown, or larger, the disease specially attacks the follicles, and produces horny balls, which are not unlike those in Pityriasis rubra pilaris, first looking yellowish-red, then taking on a chalky white colour. These mortar-drop-like balls run together to form, with the inter-follicular scales, peculiar, large, bent shields, one or more of which are placed in the middle of the brownish areas. After elevation of the border, they are easily removed, and are seen to be hollow and dotted on the inner side with a large number of regularly arranged, thorn-like, horny bodies, which regularly increase in size, from the border towards the middle, and represent the horny balls drawn out of the follicles. On the head the hairs are enclosed in bundles by yellowish-white, waxy, horny frills, an inch long, which all run together to form a yellowish-white cap, closely adhering to the head.

The anatomical investigation of this affection is as yet limited only

to the striking secondary products of the disease, the horny shields. These have no resemblance to any other known form of scale. Their hollow form developes, as the clinical observation of the retraction of the skin after their removal, teaches, from the fact that the outer border finds resistance to its extension, while the inner parts continue to grow. This surface extension depends mostly on the production of horn by the follicle mouths, whereby certain horny balls develope, extend actively outwards, elevate themselves over the level of the skin, and then run together at their bases. In the inter-follicular parts, relatively little horny substance is formed, and so the scale grows outwards as a relatively thin shell, always becoming hollower and more bent, and showing terraced processes, which rest on the isolated horny balls of the follicles, as on pillars. Inside the latter there is a regular replacement of the hairs, which are often unequal in their calibre. This shows, firstly, that the follicle is not affected, deep down, by parakeratosis, and that, during the inflammatory process, it increases in calibre. A further confirmation is, that the hairs may become grey and dry, but, in spite of their being surrounded with horny shields, do not become less numerous.

The examination of the scales for fungi has up to now had a negative result, which so far only means that the coarser, well-known hyphomycetes are certainly absent (trichophyton, varieties of favus, etc.).

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Keratosis suprafollicularis (alba et rubra).

The file-like collection of horny cones at the mouths of the follicles, on the extensor sides of the extremities, everywhere familiar under Bazin's old name Lichen pilaris, is an instructive demonstration how clinical observation, unsupported by anatomical examination, often errs about the simplest things. While the affection is regarded by Neumann "as hardly a disease," most authors regard it as such. The majority of them regard it as an epidermoidal hypertrophy, either "sui generis" (Duhring, McCall Anderson), as an affection resembling Ichthyosis (Auspitz), or as the mildest form of Ichthyosis (Kaposi). But of recent years the view, often put forward, has rightly won many followers, that in this usually non-inflammatory-looking affection, we have to do with a chronic inflammation, localised at the follicular exits, and whose more frequent, apparently non-inflammatory form has something of the same relation to the evidently inflammatory, as Pityriasis capitis has to seborrhœic eczema of the scalp. We owe to Brocq the recognition of the indistinct transitions between his Keratosis pilaris alba and Keratosis pilaris rubra. This view completely corresponds to mine, only I do not go so far as Brocq, who, under the definition of Keratosis pilaris, also includes that form, which terminates in complete atrophy of the inter-follicular cutis, regarding it as the highest degree.

I regard this as an independent disease, *Ulerythema ophryogenes*, and consider it with the ulerythemata. Crocker also, the only author who has examined Lichen pilaris, regards it as a follicular inflammation, and describes and figures (Fig. 20) a considerable collection of leucocytes in the neighbourhood of the follicle. But we must not overlook the fact that Crocker describes, under the same name, Lichen pilaris, a quite distinct disease, *Keratosis follicularis spinulosa* (Lichen spinulosus Devergie), not limited to the extensor surfaces, which, since it presents clinical and distinct anatomical differences, I also separate from Keratosis supra-follicularis; and that he, on the other hand, discusses the ordinary Lichen pilaris under Keratosis pilaris and regards it as non-inflammatory.

Clinically one finds in this affection, on the extensor sides of the extremities, especially of the upper arms and thighs, more rarely on the rest of the body, the mouths of the follicles diffusely covered with small horny cones or cone-like scales, after whose removal, a rolled-up lanugo hair is visible. The papillary elevations thus induced, are further increased by a certain degree of permanent erection of the follicles (goose skin); they are of the size of a mustard seed or smaller, of the colour of the rest of the skin, or more or less reddened. The inter-follicular skin may also share in this hyperæmia. But there is neither atrophy of the inter-follicular cutis, nor of the follicle itself. The hyperkeratosis of the follicular mouths in some cases extends into a slight general hyperkeratosis of the extensor surfaces, but it does not present the characteristic scales of Ichthyosis nitida, and the follicular changes in Ichthyosis and in Keratosis supra-follicularis are completely different.

Before I give a resumé of the histological appearances from eight corresponding cases of Keratosis supra-follicularis, I would note that, in looking out clinical material for the examination of this affection, we must be particularly careful. Of eleven cases taken from the corpse, three had to be refused; one was Keratosis follicularis, another a unique, unknown keratosis, and another, Lichen ruber.

The peculiarity of the keratosis, which we are considering, lies in the limitation of the primary change to the *horny layer of the follicular entrance* and its immediate neighbourhood. Only in a few cases was there added to this, a general thickening of the horny layer of the surface. But the cases are to be altogether excluded, in which the hyperkeratosis goes down into the neck of the follicle, and transforms it into a widely-open filter. The external mouth of the follicle remains, on the contrary, in this affection, relatively narrow; not much wider than normal, of normal width or even less. The horny layer, which is here regularly thickened, runs completely over the entrance, and must be peculiarly firm, since, in contrast to most other keratoses, it absolutely *blocks up* the follicle neck. There is, indeed, a dilatation of the follicle neck, but it is only *secondary*, from the *stagnation* in it of the normally formed contents. While the true hyperkeratoses of the follicular neck (Keratosis follicularis, Acne punctata, Pityriasis amyanthacea, Parakeratosis scutularis, etc.) dilate it considerably and almost always in diminishing degree, leading to the development of

wedge-shaped layers of horny shells, the dilatation of the follicle neck, in this affection, is only moderate, and tends to be *cylindrical.* The contents do not consist of closely-pressed horny layers, but of a few loosely arranged layers, and the main force, which causes the mechanical dilatation, is the stiff hair shaft, which cannot make its way outwards, and is therefore compelled to undergo spiral twisting. *These hair spirals hold the yielding walls of the follicular neck asunder,* and it forms a closed sack for the uppermost end of the hair.

But the hair is not in all cases completely enclosed in the follicle; very often it reaches out of the opening, and is first arrested by the horny layer heaped up over the follicle mouth. It then describes its spiral inside the horny layer, only with a much greater radius than in the follicle. As the hair and the encapsuling horny layer increase, they dig out a hole over the follicle entrance, and thus dilate the uppermost segment of the follicle neck, by flattening it out to a concave surface. The remainder of the follicle neck is generally not even dilated. However different these deformities of the follicular neck appear at the first glance, both are due to the same principle; *supra-follicular* keratosis and *retention* of the *hair.*

The retention and spiral twisting of the stiff hair shaft have still more wide-spread results on the contents and the surroundings of the follicle, which are very characteristic of this affection. It is remarkable that the middle and under third of the hair follicle, as well as the sebaceous gland, with its epithelial contents, are not directly affected by the process, and remain completely normal. But indirectly they are severely injured, for the spiral twistings of the hair shaft extend to the middle third, and thus the prickle layer in this situation is irregularly pushed aside. In general the hair shaft, along with its root sheath, leaves the central axis for a peripheral position, and therefore appears in section, now on the right, now on the left, near the wall, while the remaining space is occupied by the displaced prickle layer. In the under third of the follicle, where the hair is rooted, it retains its central position. One finds, therefore, a number of hair follicles, in which there are, from above downwards, a cylindrical hair cyst, then a hair spiral, irregularly penetrating the prickle layer, and finally the normal lower end of the hair, with the papilla.

Most of the lanugo hairs in this affection are in the bed hair stage, and the hair bed itself occupies the under end of the middle third. We frequently have in these cases an epithelial process, certainly very small, but normally formed, and usually in relation to a papilla; the hair bed is also normal, and the hair spiral first begins, a considerable distance higher up, it may be in the prickle layer, in the widened neck, or above the follicle mouth. This invariably corroborative discovery

of bed hairs, seated firmly in the hair bed, in this affection is evidence that the bed hairs are not hairs already cast, and lying loose in the follicles, for then they would be also spirally twisted and elevated from their bed by the enormous force which causes the twisting of the hair shaft.

But not only are the epithelial contents of the middle part of the follicle completely displaced, the whole follicle undergoes, although in lesser degree, a *spiral twisting*, which follows the twisting of the hair follicle. Consequently, successful sections which show the cystically dilated neck and the under third of the hair, show only single segments and lateral portions of the middle third, for here the greater part of the twisting follicle is outside the plane of the section. The segments are then of an elliptical, triangular, pear shape, and show, in one or more corners, the cross sections of the hair.

But the mechanical deformities of the hair are not yet exhausted. To the *mechanism of retention, there is further added the action of a hypertrophic muscular apparatus.* Evidently the resistance which the hair experiences to its escape, and which causes a packing or tension on the under end of the follicle, induces reflexly a permanent irritation of the arrector muscles, which, of course, are also stretched, since their under end is inserted into the middle third of the follicle. It is thus very clear why all the arrectors are strikingly large, broad, have many insertions, and are distinctly hypertrophic. This one-sided and external new force leads to certain of the follicles being sharply *bent* as well as twisted.

The hair muscle endeavours to elevate, once more, the lower end of the follicle, which has been twisted and pushed down by the hair spiral, but without achieving its aim, the escape of the hair point from the follicle. Under favourable circumstances—that is, where the hair muscle is very vigorously developed, and the upper part of the hair follicle has been elongated by the hair spiral, and is, therefore, easily pushed aside—the under third of the follicle is bent at a distinct angle to the other two thirds. Usually the cylindrical funnel then runs outwards near the arrector, and in the same oblique direction, and passes into the middle third, which shows the spirally-twisted hair inside the prickle layer. But this third immediately bends, from the upper, towards the arrector, and when it reaches that, is again bent in an opposite direction, so that the under third comes to lie directly in the direction of the muscle. The muscle, attached between the middle and under third, and drawing this point outwards, has converted these two parts of the hair follicle into the two limbs of an angle. Thus it is not wonderful that the elongated hair shaft, supporting the walls, should press on the bends, tend to break through,

and here and there actually do so. All these deformities, which, at the first glance, appear so remarkable, are simply explained by the forces of hair retention and by the muscular reaction, apparently necessary for its removal, but really acting in the opposite way.

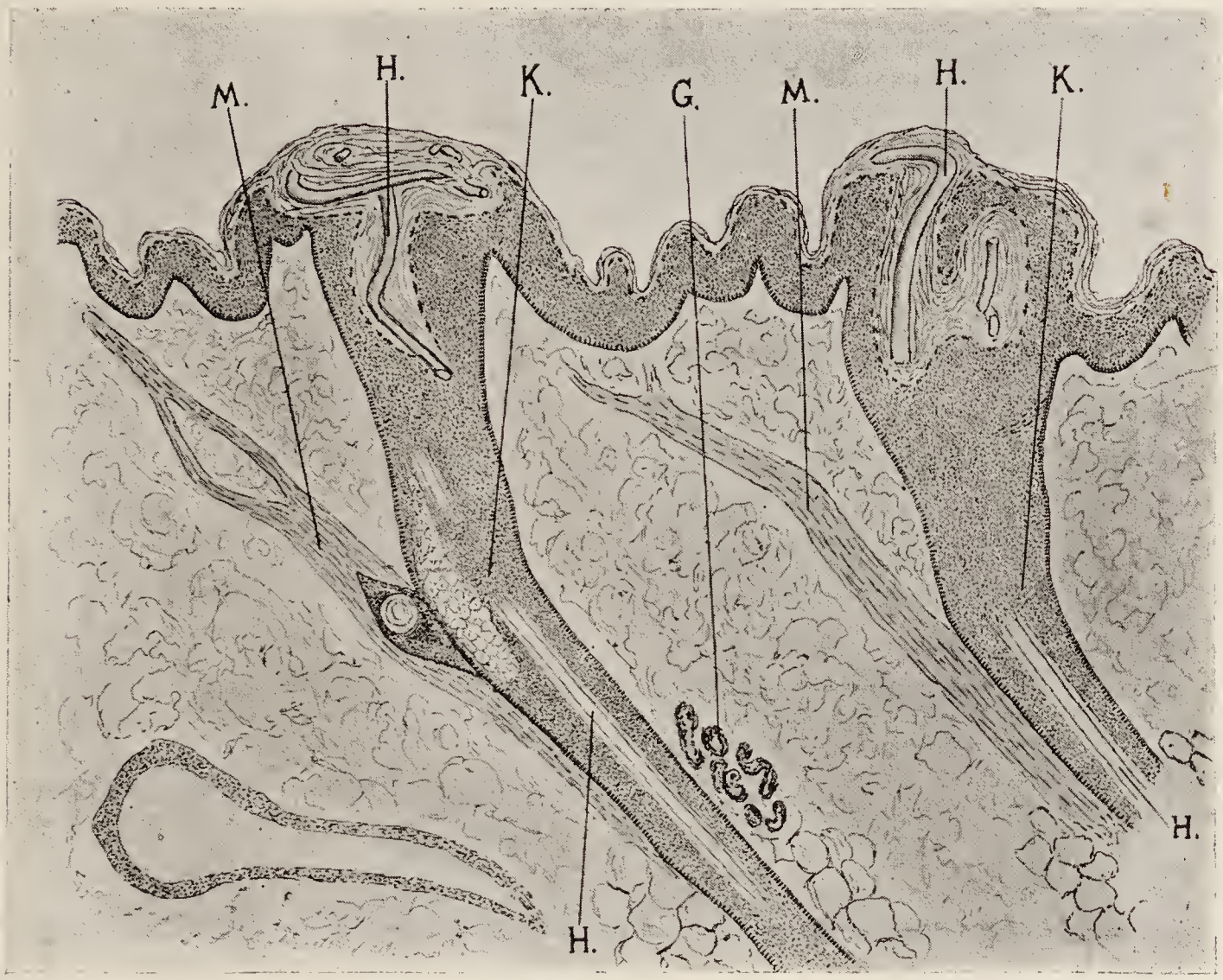

FIG. 11.—Sketch of Keratosis supra-follicularis.

H. Hair, coiled up at the surface.
M. Muscles,
G. Coil gland.
K. Bend in the follicle caused by action of the Muscle.

Where the arrector causes no bending, one usually sees an epithelial process arising in its direction, into which it is inserted ; and this very often contains a homogeneous, clear, horny pearl. The epithelial processes, extending outwards underneath the bed hairs, are always small and only rarely productive ; I have only once observed a young hair in one of them. The constant pressure on the germinal layer appears, in spite of the normal condition of the epithelium in the under third, to be unfavourable to the formation of new hair. In the hair cysts of the upper third, we only rarely find one or two cast hairs, in spite of the long undisturbed condition of the papules—a striking contrast to Acne and Parakeratosis scutularis, where, almost always, several cast hairs are retained in the follicle. The sebaceous glands are sometimes

normal, but usually they atrophy, and we never find, as in the comedones of Acne, a marked amount of fat in the hair cysts. The coil glands appear to be unchanged; the horny layer at the sweat pore frequently shows a thickening, like the follicular mouths.

In my preparations, the relations of the cutis are very varied in regard to the number of cells and the width of the blood vessels. The latter are, in the majority of cases, not dilated, but now and again they are distinctly so; not only those around the follicles, but also all the superficial ones. In almost all cases their perithelium is increased and multiplied, but only rarely so much, that one can speak of cellular vessel cords. The cells do not go beyond the spindle form. Plasma cells are not found, but mast cells are more abundant than normal. These latter are especially numerous around the follicle, and are distinguished by their more rounded than stretched form, and many small notched processes; one often finds multi-nuclear mast cells and round connective tissue cells, which partly show the specific granulation. In addition to the surroundings of the vessels, those of the follicle and the wall of the follicle itself are more cellular, which, considering the mechanical lesion of the follicle, is not remarkable. Now and again, especially at the follicle neck and at the bent part, the collagenous substance of the hair follicle also appears slightly changed, it retains basic colours more than normal and appears diffusely stained, when the collagen of the cutis is completely decolourised. I once found the collagenous intra-cellular substance of the fatty tissue mucoid.

The histological examination consequently corresponds completely to clinical observation. The lid-like horny scales correspond to the hairs, with the hair spiral in the cylindrically dilated filter; the horny cover proper, to those with the spiral inside the horny layer of the follicle mouth. The hypertrophy and hypersthenia of the arrectors sufficiently explain the erection of the horny papule. The affection is certainly inflammatory, for there is present always slight, sometimes pronounced perifollicular and inter-follicular new formation of connective tissue cells, and in about a third of the cases, permanent dilatation of the vessels. But I could never find a local leucocytosis around the follicle, as Crocker did in his "Lichen pilaris." In the differential diagnosis of Keratosis supra-follicularis, one must pay special attention to the supra-follicular character of the change, the appearances of retention, the almost cylindrical dilatation of the filter, the spiral hairs, which are never absent in fully-developed papules, the bending and twisting of the follicle, and other deformities of a secondary nature. In these relations *Keratosis supra-follicularis* has more resemblance to Favus than to most other keratoses, and should not be histologically confused with them.

LITERATURE.

Text-books of Brocq, and the authors named in the text.
Crocker, Text-book, pp. 228 and 298.

Pityriasis rubra pilaris.

The knowledge of this affection we owe entirely to the French school—Devergie, Richaud, and especially Besnier. Usually following a keratosis of the plantar or palmar surfaces, a seborrhœic catarrh of the scalp and a pityriasis of the face, there appear, on the trunk and extremities, the characteristic lesions around the follicles, and, gradually extending from above downwards, they affect in different degrees the greater part of the body, without causing any injury to the general health. These follicular elementary lesions are masses of horn, surrounding the hairs, about the size of a turnip- or mustard-seed, they are covered with snowy white or greyish horny scales, and look like drops of lime; they are arranged in groups and feel like a file. They are especially characteristic where they appear in small areas, corresponding to a circumscribed group of hair follicles, *e.g.*, on the extensor side of the first phalanx. Other small horny masses correspond to the sweat pores; others are quite independent of the normal openings.

Equally important in the diagnosis, as the circumscribed horny masses, is a *general hyperkeratosis* of the surface, which is shown in the thickening of the horny layer and the coarseness of the lines, especially on the extensor surfaces of the extremities. Owing to the disappearance of the finer furrows, there are seen large areas, which are sometimes smooth and shiny (shoulders), and have here and there, in their middle, mortar or plaster-like heaps of scales (extensor surfaces of the arms and legs).

The third important symptom is a marked persistent *redness of the skin, without a corresponding inflammatory infiltration.* On parts which are normally moister (face, neck, elbows, knees, and genitals), it appears diffuse, combined with slight thickening and scaling of the horny layer, and thus there is developed a resemblance to Pityriasis rubra Hebra. But on the predilection seats of the horny masses, especially on the extensor surfaces of the extremities, it is restricted to the horny masses and surrounds them with a hyperæmic border, and further, it affects the larger scaly surfaces, which have arisen from the follicular elements, by the running together of the horny layer, and surrounds them also with a red halo. The hyperæmia is not present everywhere; in some patches it is masked by the thick scales. According to the development of scales, the erythematous spots resemble Psoriasis or Ichthyosis; from the former they are distinguished by the presence of

horny balls, from the latter by the light, often chalky white colour of the scales, and their follicular distribution.

From these clinical symptoms, combined with more or less seborrhœic catarrh of the scalp, which is perhaps accidental, is composed the multiform eruption, which characterises the affection, and which, in individual cases, may undergo striking modifications. I owe to Professor Düring (Constantinople), two pieces of skin, one from a recent, and one from an older case; and to Professor Audry (Toulouse), a piece of an old psoriatiform plaque. The former shows the character of the elementary papule, the latter the changes inside the older patches. But these pieces of skin are not sufficiently conclusive regarding the pityriasis rubra-like character of the skin of the face and of the contact surfaces, the *specific Erythrodermia*, and, further, the *stalactiform patches*, which arise, by confluence of horny balls, at the elbows and knees, so that we must temporarily construct their character from the anatomical characters of the other eruptions.

We have, according to my available material, to describe the following elementary forms:—

I. Simple elementary forms—
- (1). Follicular papule.
- (2). Poral papule.
- (3). Sinuous papule.

II. Synanthems—
- (4). Erythrodermia.
- (5). Psoriatiform patches.
- (6). Stalactiform patches.

Since the Pityriasis rubra pilaris of earlier authors is often described as Lichen ruber, in describing this form I will always keep in mind the comparative anatomy of Lichen.

1. *Follicular papule.*

The follicular papule of Pityriasis rubra pilaris always appears—in contrast to that of Lichen—as part of a *general, primary, very marked hyperkeratosis.* Just as, in Acne punctata, the comedones are usually regarded as the only diseased areas—the diffuse thickening of the horny layer, which is their cause, being ignored—so in pityriasis pilaris, the horny cones, covered with mortar-like scales, at the mouths of the follicles, have attracted most attention. But not only are these, here also, only a part of a diffuse hyperkeratosis, but this latter leads, on other places as well as the follicles, to well-characterised papules, though clinically they are certainly less striking. We must, therefore, first give our attention to the diffuse changes of the surface. The prickle layer is not greatly, but equally widened, the granular layer consists of two or three rows and is therefore much thickened, and the horny layer is twice or thrice as thick as normal. But it is not only thickened. It is also markedly increased in *its surface extension.* This surface extension is an

appearance, which is by no means present in every hyperkeratosis; it can only be present in those forms which are not accompanied by permanent scaling. Its result is, that the horny covering, as a whole, becomes too large, and the prickle layer, with the papillary body, is thrown into coarse folds, which take the place of the vanished, finer, epidermic furrows, and partly that of the coarser epidermic furrows, though the folding leads also to new furrows. The prickle cells are enlarged, the inter-spinal spaces somewhat dilated; these changes also are—in contrast to Lichen—not anywhere excessive, but more equal and further extended. There is never here—as in Lichen—loss of the prickles, great œdema spaces at the border between the cutis and epithelium, or colloid degeneration of the epithelium. Corresponding to these epithelial appearances, the papillary body in Pityriasis rubra pilaris is only slightly cellular; the papillæ are but little swollen, and not œdematous; there is no hyalin metamorphosis, no sclerosis of the collagenous tissue, and never, as in Lichen, a continuous band of condensed sub-epithelial cellular infiltration.

On such a surface, characterised by severe hyperkeratosis and moderate inflammation of the papillary body and the prickle layer, the follicular papules are now developed. The horny layer runs over them, and sinks into the follicle necks. In many follicles it extends in its full breadth to the base of the lanugo hair follicles, in others only to the base of the follicle neck. In no case does the hair directly suffer; it is either retained in the follicle, bent or spirally twisted, or it at once falls out. The new formation of hair, however, suffers from the simple hyperkeratosis of the follicular epithelium, but not in the same way as it does in the lichenous process. It is specially these follicles, in which only the neck is filled with horny layer and the prickle layer of the upper part of the follicle at the same time proliferates, which can give rise to the formation of typical horny cones. Here we do not find, round the follicle entrance, excessively swollen papillæ, which lead to the elevation of the papule, the formation of "cutis anserina," as in Lichen; the elevation depends solely on a moderate hypertrophy of the prickle layer, and a considerable collection of horny masses in and over the follicular entrance; the follicular papule of Lichen is chiefly cutaneous, that of Pityriasis rubra pilaris purely epidermic (v. Düring). In spite of the much increased hyperkeratosis in the follicular neck, I have never, on my preparations, seen developed the regular formation of folds, like a paper filter, which is seen in Lichen. Instead of these there are formed very voluminous, onion scale-like bodies and horny pearls, with or without hairs in them. This is the more striking, as on the surface the voluminous horny layer is very distinctly folded.

The cellular infiltration round about the follicles is greater than in the follicular lichen papule; it is not limited to the upper part of the follicle, but is developed throughout its whole length, and almost invariably forms dense collections in the middle and lower papillary part. The cells are not so invariably small and poor in protoplasm as in Lichen, but are well-developed spindle cells; the areas enclose a few plasma cells, and rather more mast cells. Where they lie on the wall of the follicle, there is usually a circumscribed, inter-epithelial œdema of the prickle layer of the follicle, and a local leucocytosis, limited to a small area of the prickle layer of the follicle. White blood corpuscles are also regularly found inside the cellular areas, outside the follicle, but in general they are only sparing in the skin. This circumscribed œdematous swelling, with leucocytosis of the follicle epithelium, is here and there present, without marked perifollicular areas, and is present, irregularly, in the prickle layer of the surface. To this latter there usually, but not always, corresponds a marked cellular infiltration of the adjacent papillary region.

In cases of such distinct exudation in the hair follicle, one occasionally, though certainly only rarely, finds flattenings and deformities of the hair shaft and the root sheath. In spite of this inflammation, so marked at certain parts of the follicular epithelium, there is none of the sclerotic change of the follicle membrane, with loosening of the prickle layer in the upper part of the hair follicle, which is present in Lichen. *The processes in Pityriasis rubra pilaris always indicate a purely progressive inflammatory character;* those in Lichen possess a mainly regressive inflammatory character. Therefore it is not surprising, that, in some hair follicles, the prickle layer shows projecting thickenings, but this is never a prominent histological appearance, still less a characteristic of the disease.

This is the place to consider a statement which is found in all the text-books, and which was originally made by I. Neumann. He found in Hebra's "Lichen ruber exudativus" (1868) many *out-growths of the external root sheath—i.e.*, of the prickle layer of the hair follicle. As we now know, most of these cases were Pityriasis rubra pilaris, and it is probable that Neumann's statement relates to such a case, and not to one of Lichen as we now regard it. For the follicular papules of Lichen, which are chiefly present in Lichen neuroticus, show almost pure regressive changes, and certainly no tendency to out-growths. In this symptom there is certainly nothing lichenous, but it is also in no way characteristic of Pityriasis rubra pilaris. Possibly by it is understood the ordinary proliferation of the hair bed, which sets in when the renewal of the hair is made more difficult, if the proliferating process has the courage to attack once more the old follicle; this also can, in

Pityriasis rubra pilaris, only be present on hairy regions, while it often accompanies many other affections — for example, many seborrhœic alopecias. Like this statement, on which Kaposi founded the lichenous nature of his Lichen moniliformis, all the older conditions found in "Lichen" require fresh proof as to their occurrence in Pit. rub. pil., and must no longer be simply worked in with the present views on Lichen.

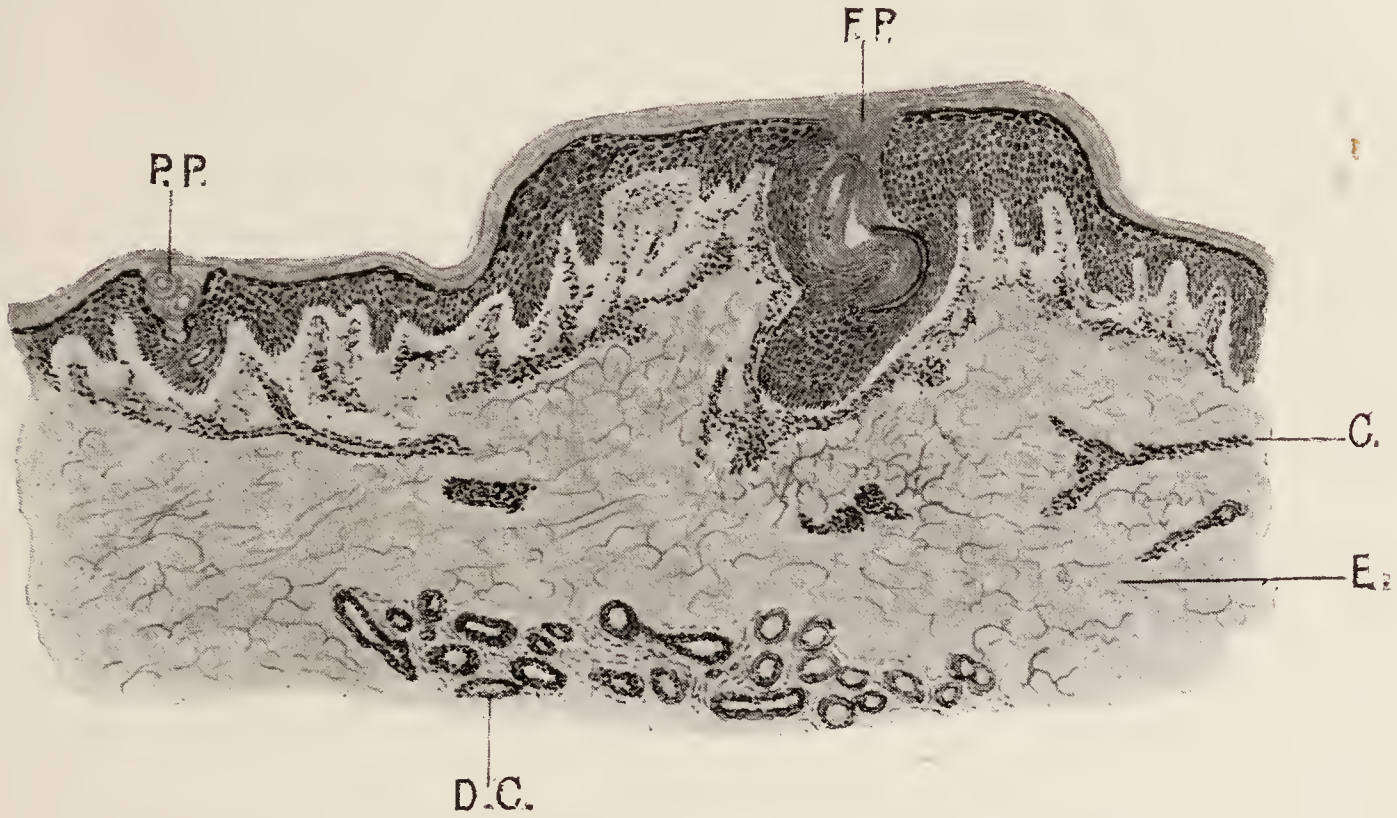

FIG. 12.—Pityriasis rubra pilaris.

P.P. Poral papule. *F.P.* Follicular papule.
E. Elastin. *D.C.* Dilated coil gland.
C. Capillary.

2. *Poral Papule.*

Much less characteristic of Pityriasis rubra pilaris than the follicular papules, are those which form around the sweat pores. The presence of isolated, plaster-like collections of scales on the palm of the hand indicates their existence. Histologically, we learn much more, where we have to do clinically with isolated horny cones, of somewhat smaller calibre, than is usual in the follicular papules. At the commencement they differ little from the poral papules of Lichen obtusus. The growth of the epithelial cells, lying around the sweat pores, is all along more distinct, and the infiltration of the papillary body less. Further, they are distinguished—in addition to the absence of the familiar degenerative processes of Lichen—by a much lesser tendency to the formation of concentric horny pearls, though that is also present in the older, especially the psoriatiform patches. But the

younger ones only show a more or less marked thickening of the spirally twisted horny filter, which sinks into the sweat pore. They have consequently more a histological than a clinical significance.

3. *Sinuous Papule.*

On the contrary, very characteristic of Pityriasis rubra pilaris, are certain papules, which, on account of a marked depression of the horny layer in their centre, I call Sinuous papules. Of their clinical significance and character, I have, from the little material available, formed no judgment. But they are certainly characteristic histologically, for in them the superficial increase of the horny layer has reached striking dimensions; and therefore these papules also have no counterpart in the lichenous process. There is a reactive epithelial growth on the basis of a deep penetrating fold of horny layer, which, on the one hand, penetrates into the cutis in thick blunt processes, and on the other distends the horny layer on both sides of the fold, like a buckler. This, like the granular layer, is much thickened, and aids in elevating the papule. This dry, broad, conical papule may further be covered by a scale, soaked in serofibrinous exudation. In the centre of the papule there is neither sweat pore nor follicular opening; but these may be found enclosed at the margins of the papule. The blood vessels underneath these papules are very markedly dilated, while the cellular infiltration is, as usual, moderately developed. The capillaries which lie in the papillæ, separated by the epithelial processes, fill them almost completely, and give the impression of telangiectatic vessels. This dilatation is evidently of mechanical origin and dependent on the deep fold of horny layer; possibly this local stagnation of blood at the periphery also favours the marked acanthosis at the base of the fold; at all events it favours a leucocytosis, and slight serofibrinous exudation, which appears, here and there, in relation to single papillæ, and which is in direct connection with the inflammatory crusts at the summit of the papule.

It is very probable that part of the hyperæmic halo, which surrounds the papules and the patches of Pityriasis rubra pilaris, is to be attributed to such a stagnation, caused by the pressure of the swelling and folded horny layer.

4. *Erythrodermia.*

The parts, distinguished by redness and a rough, scaling, often plastered-looking, but little scaling epidermis, still require examina-

tion. But we may say, from the whole character of the affection, that they may certainly be distinguished from Hebra's Pityriasis rubra, and from Pityriasis rubra seborrhoica, by two symptoms; the lesser cellular infiltration of the papillary body, and the greater coherence of the horny cells. Pityriasis rubra pilaris always gives — like Ichthyosis — the impression of a hyperkeratosis, rather than of a parakeratosis, although at individual spots of greater exudation, the typical change of the transitional cells exists; in erythrodermia, one would expect to find the parakeratosis more general. In the diagnosis, one would have to give attention to the initial appearance of the follicular and poral papules, and to certain changes of the coil glands, which are always present in the other forms of the affection; enlargement of the loops, and dilatation of the lumen. At all events, it is possible to distinguish this Erythrodermia from others.

5. *Psoriatiform Patches.*

When the individual horny cones run together into a common mass of scales, and their hyperæmic halos mingle, the follicular papule, the special characteristic of pityriasis pilaris, is lost to clinical view. And histologically, also, the perifollicular growth passes into a diffuse acanthosis of the surface; into a hypertrophy of the ridge system. At the same time the cellular infiltration of the papillary body and of the walls of the cutaneous vessels, and the dilatation of the superficial capillaries, increase, and the papillæ are lengthened, proportionately to the increase in the ridge system. Most of the papillæ increase also in breadth, and attain a somewhat plump, rounded, conical form, which is to be ascribed, in a lesser degree, to a dilatation of the capillaries, but chiefly to the dense infiltration of cells. When I further state, that the sub-papillary prickle layer remains small or even diminishes in favour of the inter-papillary, it is clear, that there is a distinct resemblance to Psoriasis and psoriatiform Eczema. Just as in these typical parakeratoses, there is found, here and there inside the epithelium, especially around the apices of the papillæ, a local leucocytosis; wandering cells, singly and in groups, press the epithelium asunder, and, as cornification proceeds, are enclosed as small nests of nuclei and nuclear fragments. Thus the otherwise firm horny layer is in parts converted into loose scales, in which streaks of nuclear fragments are entangled.

But with this, the resemblance to Psoriasis is exhausted, and we may complete our further description by comparison with Psoriasis. Certainly over many papillæ, especially where leucocytosis exists, the keratohyalin—not the elëidin in the same degree—has dis-

appeared, but not everywhere, and never in relation to the ridges lying between them. Here the granular layer is, rather, regularly thickened, and the amount of keratohyalin very considerable. And so, in sections, hyperplasia and aplasia of the granular layer alternate more or less regularly with the elevation and depression of the papillary body.

The variation is not as in psoriasis; there the diminished formation

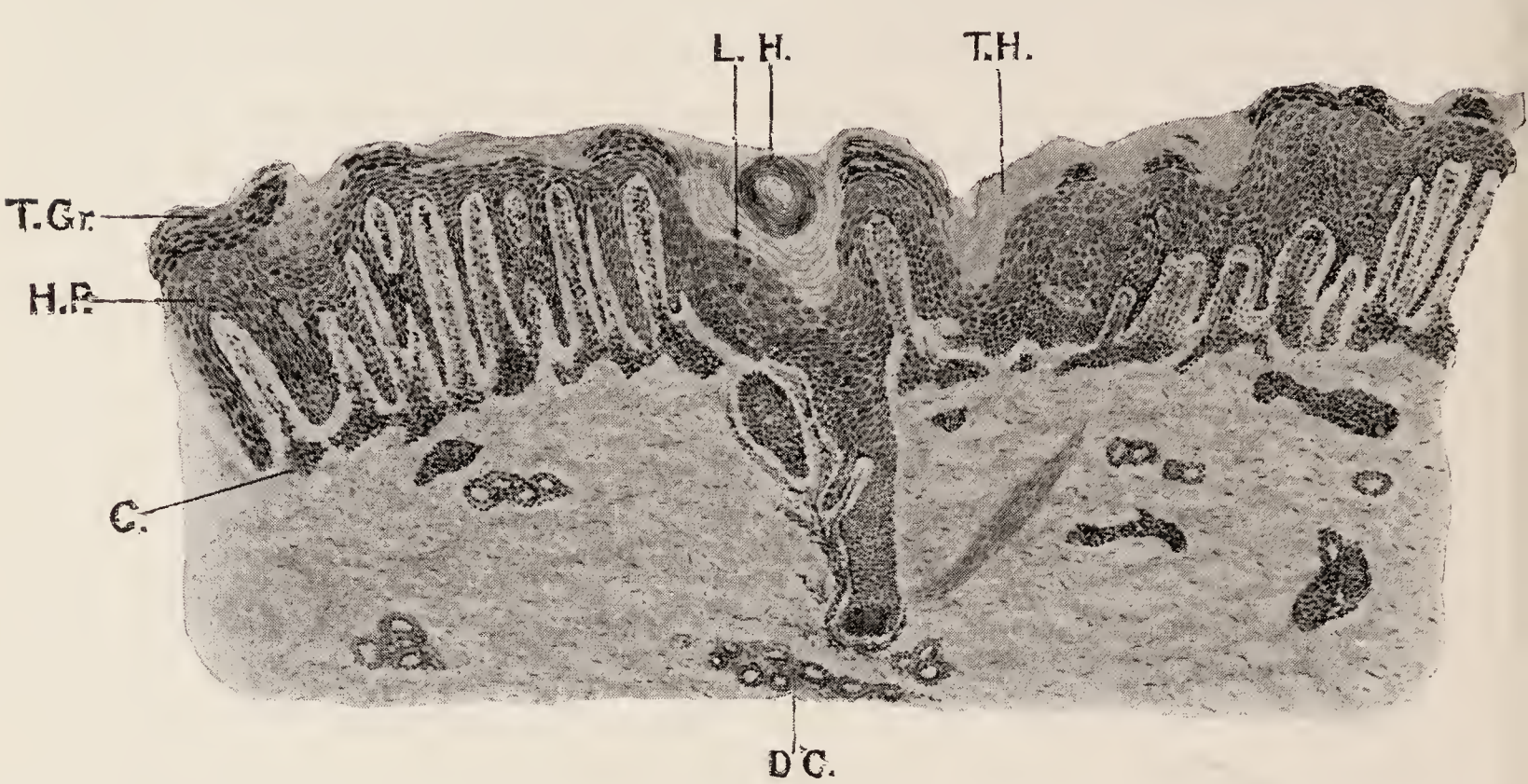

FIG. 13.—Pityriasis rubra pilaris. Psoriatiform patch.

H.P. Hypertrophic prickle layer.
T.H. Horny layer thickened.
H. Horny pearl in follicle.
L. Leucocytes in horny layer.
D.C. Dilated coil.
T.Gr. Thickened granular layer.
C. Cell infiltration of papillary body.

of keratohyalin, at the height of the affection, is the rule all over the surface, equally, and only in the new formation of scales is there at once a great collection of keratohyalin; here, on the contrary, the abnormal collection of this substance is the rule, and only where increased pressure and greater exudation meet, over the papillæ, does the keratohyalin disappear in streaks, and permanently.

Further facts of the same significance are: the regular loss of nuclei of the pityriatic horny layer, its homogeneousness and great firmness, while the psoriatic and eczematous scales are marked by their regular retention of nuclei, and their tendency to desquamation and scaling.

This structural difference of the horny substance is fundamental. On it depends the coarse *folding of the surface*, even in this form of Pityriasis rubra pilaris, and the formation of *horny taps* and *horny pearls*. These appearances make the distinction from psoriatic skin

easy, even with a low power; in the horny bodies, Pityriasis rubra pilaris again rather approaches Lichen.

The *superficial increase* of the horny layer leads to its sinking deep down inside the ridges, at distances of six to ten ridges, and consequently so many papillæ are arranged in small groups. Such a group possesses a pretty uniform, thick horny covering. Finally, the scales and crusts which form, are margined by the ridges, so that an areated appearance of the patch is developed.

The *increase in depth* or thickening of the horny layer leads, in relation to the ridges, to new layers of horny cells on the under surface of the common horny covering, and thus horny taps, like corns, gradually sink into the ridges. This result of hyperkeratosis affects only the broader ridges, so that very soon two forms can be distinguished; a great number of smaller ones, which are diminished by the thick papillæ between them, and a smaller number of broader ones, which alone contain the horny structures. These latter may be divided into simple horny pearls or horny discs, follicular horny taps, and poral horny filters or horny pearls. In the neighbourhood of these compressed, homogeneous horny structures, the adjacent prickle layer often contains a few colloid epithelial cells, and thus the resemblance to Lichen becomes still greater. But the horny layer never sinks in so deep, and the prickle layer never becomes so atrophic as in Lichen; the wide-spread appearances of degeneration are altogether absent; indeed, even the inter-spinal œdema, which, in the younger forms of Pityriasis rubra pilaris, is here and there pretty prominent, seems to disappear with the increased epithelial growth, and to be replaced by a parenchymatous change, an increase in volume of all the epithelial cells.

Nor is the deformity of the papillary body, when closely studied, so psoriasis-like as it appears at the first glance. It strikes one at once that very many broad papillæ alternate with pretty extensive a-papillary spaces. Then the form of the papillæ is not the same as in Psoriasis; they never lose, in spite of the rounding, their conical character, *i.e.*, they are, at their bases, relatively broad, while psoriatic papillæ always have a tendency to club-shape, with a contracted base. Consequently the sections of the ridges in Pityriasis rub. pil. are mostly pointed at their free ends, while those in Psoriasis tend to be rounded and club-like. These circumstances appear to depend on the fact, that the psoriasis papillæ are not distinctly infiltrated with cells in their whole length, but, on the contrary, are frequently somewhat œdematous at their apex, while those of Pityriasis rub. pil. are, as a rule, firmer, and more equally permeated by cells. This is probably to be explained in the following manner. The resistance of the papillæ, necessary

to the development of a chiefly inter-papillary prickle layer, is provided in Psoriasis by the abnormally high blood-pressure in the capillaries, in Pityriasis rubra pilaris by the cellularly infiltrated, firm tissue.

The share of the hair follicles, whose sebaceous glands are always atrophied, and the coil glands, is the same in this process as in the simple form. Only the acanthosis at the exit of the hair follicle tends to be more distinct, and the dilatation of the coil is, here and there, accompanied by proliferation of the epithelium. The cellular infiltration of the cutis is not greater, but it extends further outwards. All the blood vessels are surrounded by dense cellular strings, in which, here and there, are plasma and mast cells. The muscles are well developed.

6. *Stalactiform patches.*

The horny masses attain their highest development on the knees and elbows, and form here plaster-like, coarse, tap or conical-formed horny masses, running together at the base. According to the explanation which we have given of these conditions in the psoriatiform patch, the base of these stalactiform cones is a group of epithelial ridges, which are already united under a common horny covering. They therefore contain a closely-packed group of papillæ. The hyperæmia of these patches is no less than that of the others, but is more masked by the dense horny layer. Everything further must be left to future investigation.

From this description, in which I have given special attention to the differential diagnosis from Lichen and Psoriasis, it is evident that Pityriasis rubra pilaris possesses most resemblance to the severer forms of Ichthyosis. It stands like that disease on the borders of the parakeratoses; in both of them the hyperkeratosis, if inflammatory congestion be added, passes into the ordinary appearances of parakeratosis. The differential diagnosis from Ichthyosis, I will give in the description of that disease.

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Lichen.

General review of the Lichenous process.

By Lichen, I understand only that diseased process of the skin, first described by E. Wilson, which, but a few years ago, under Wilson's name "Lichen Planus," there was a tendency to set against the "Lichen ruber" of the older Hebra and the "Lichen acuminatus" of Kaposi. But as it was apparent, at the International Dermatological Congress in Paris in 1889, that Kaposi wished to include, under his "Lichen acuminatus," the same disease which Devergie had already described as "*Pityriasis rubra pilaris*," and as, on the other hand, it is by no means clear what Hebra senior called "Lichen ruber" (Hebra jr. contra Kaposi, Paris Congress), Wilson's Lichen is, with the exception of Pityriasis rubra pilaris Devergie, the only well-characterised affection remaining of the old group. In order not to reawaken past strife and confusion, it is better to avoid the adjective "ruber," although it is applicable to most cases of Wilson's Lichen.

The clearness and simplicity of the clinical standpoint thus attained, is all the more valuable, as Lichen thus restricted, in spite of its many modifications, presents, *histologically, a very well-defined unity.* I cannot, therefore, regard with favour the restitution of the older definition of Lichen by the younger French school (Vidal, Brocq),* in which quite different anatomical processes are present, and for which other excellent clinical names exist. Without this, the simple Lichen, which represents an extension of Wilson's Lichen planus, contains quite a sufficient number of different forms. Finally, for the same reason, I separate also from Hebra's old Lichen group, Lichen scrophulosorum, under the name *Folliculitis scrophulosorum.*

The limited and purified Lichen represents—like Eczema and Syphilis—a polymorphous group of eruptions, in which a uniform complex of symptoms forms, both clinically and histologically, the base.

Clinically all forms of Lichen are characterised by a bluish-red firm papule, which is covered by a very firm, thickened, stretched, shiny horny layer, shows no development into vesicles and pustules, no persistent scaling, but, on the contrary, tends to the development of horny pearls, horny grooves, and thick horny plates. It is accompanied by more or less severe itching, appears in groups or patches, and is usually very chronic. The power of extension of the individual papules is limited; they leave behind them, after healing, more or less pigment.

* Lichen simplex aigu et chronique Vidal, Lichen polymorphe ferox Vidal (=Prurigo Hebra).

The smallest papules (1-2 mm. diameter) usually show a straight-lined, angled, *polygonal contour*, which alone, when present, justifies the diagnosis, Lichen. This contour remains only rarely during their enlargement, more often in their confluence. The papules elevate themselves sharply from the pre-existing furrows, and it is these which give the multi-angular contour. These miliary to pepper-corn-sized papules are usually universally distributed, especially on the wrist, joints, backs of the hands, fore-arms, the legs, the abdomen, the neck, and the genitals.

Or there develope, from the commencement, *larger papules* (5-7 mm.) of *rounder form*, which are not sharply, but gradually elevated from the surroundings, and carry in their centre a small horny pearl, or a depression, corresponding to a sweat pore. These "*obtuse*" papules are smooth, shining, do not scale, and have a transparent look.

They often increase pretty considerably, but tend at the same time to be flattened out. They are often present in large quantity, but are never so numerous as the miliary papules. It is almost the only form which occurs in infants and young children.

Not so frequent as one would conclude from the older name Lichen planus, is the form of the perfectly *flat* papule, which shows bluish or brownish red, just over the level of the skin, or is hardly at all elevated, and even presents a slightly sunken spot of specific hardness, and burnish. Very characteristic of this form, are white mother-of-pearl points, which shine through the horny layer; at these places one may dig out from the epidermis "milium-like" horny pearls, without causing bleeding. The flat Lichen papules usually appear on the leg, mostly only in limited numbers, but they also appear on other parts of the body, even on the palm of the hand, sole of the foot, and the hairy scalp, where the other forms of Lichen are rarer. They have a tendency to form larger patches, by increase and confluence, to form above varicose veins, and to leave behind them much pigment.

The *corneal* or *keratoid* papule is a modification of the plane Lichen papule, which is mostly seen singly, on the leg. It projects distinctly over the level of the skin, partly owing to a marked infiltration of the cutis, partly owing to epithelial hypertrophy and thickened horny layer, which is folded in many directions, and includes horny pearls and horny taps. It itches severely, and is of very long duration.

The *atrophic papules* develope on the leg, along with the plane and corneal forms. They are sunk beneath the level of the skin, surrounded by a somewhat elevated and shiny border, are rosy red or white, like mother-of-pearl, covered by a fine folded, thin, horny layer, and are usually surrounded by a halo of pigment.

The *ring-formed* papules appear in two different forms. Here

and there, in large, disc-shaped, flat papules, there is a serpiginous extension of the (5 mm. broad) elevated margin, while the centre sinks in, heals, and becomes pigmented. This annular form may be only partially developed, only one part of the edge becoming serpiginous. The development is always limited (especially on the leg), and never affects all the spots, being merely accidental.

A second form of the *ring-formed papule is substantial*, that is, it is present in all the spots, and is very different in size; it developes from plane papules, of the size of a lentil to a pea, by the extension of a very small (1 mm.) border, while behind this fine, shining, delicate, ring-formed ridge, the papule at once becomes flattened. The whole papule then consists only of an excessively fine, but hard and smooth, bluish-grey or reddish-grey ring. This form of Lichen is sometimes found limited to the genitals, sometimes as a universal eruption, in which case it is more chronic and pigmented.

The eruptions of elementary and combined form, hitherto described, are combined in different ways to form the ordinary, more or less extensive, or regionally limited, chronic cases of Lichen. But there is also an acutely developing, universal form of Lichen, which is distinguished from all others, on the one hand, by extensive, severe, nervous symptoms and disturbance of the general condition, on the other, on the skin, by the diffuse extension of the process, in the form of a slightly-scaling *erythrodermia*, and of follicular, scaly or smooth, conical papules, at the follicles of the affected regions. It shows itself a true Lichen, clinically, by the ultimate appearance of plane Lichen papules and patches; and the difference is evident histologically. It is the form which I have described as *Lichen neuroticus*. On account of the graver prognosis of this form, it may very well represent Hebra's original, severe, mostly fatal cases of Lichen ruber.

The reconstruction of these clinical forms, from the histological factors, is best carried out, as in all polymorphous eruptions, by viewing them as combinations of simple and combined elementary forms. It is the latter which admit of a direct and exact histological explanation, and from their various combinations the disease developes. The simple elementary forms of Lichen are the *polygonal*, *obtuse*, *plane* and *follicular papules*; the combined elementary forms (or Synanthems) are, the *Lichen rings*, the *Lichen patches*, and the *Erythrodermiæ*. From the plane papule are developed the corneal (hypertrophic, verrucous) and the atrophic (sclerotic). The Lichen rings break up into the papulæ gyratæ et annulares, the Lichen patches into the plane, verrucous and sclerotic. Erythrodermia has been the least investigated; we find in it both plane papules and remains of follicular papules.

In every elementary form of Lichen, there concur at least two

groups of changes, those of the epithelium, and of the papillary body, and in many there is a third, in the coil glands.

In the epithelium, we find, first, a simple hyperplasia of the prickle layer. The epithelial ridges are consequently now and again powerfully developed, but are, as a rule, flattened, and run together into a flat plate, often leading to the complete levelling of the margin between epithelium and cutis. The lymph tracks of the prickle layer are frequently much dilated, sometimes like ampullæ, they are always wider than normal, and are connected directly with the dilated lymph spaces of the cutis. To the acanthosis there is added a hyperkeratosis, with delayed cornification; the granular and horny layers are thickened, especially the basal part of the latter. Since the proliferation of the prickle layer gradually diminishes, while the tendency to the formation of a specially firmly connected horny layer persists, the horny layer, especially in the centre of the papule, sinks into the broadened ridges, is always margined by an abnormally broad granular layer, and increases at the cost of the prickle layer alone, which is here always thin, and is finally reduced to quite a small plate. In this way develope the concentrically arranged horny taps and horny wedges, quite independent of all lanugo hair follicles. The sweat pores penetrate the prickle layer unchanged, or, at most, there is a proliferation of the prickle cells in their neighbourhood. But in the horny layer, the epithelium of their walls has run together into horny clumps, with the staining reaction and the consistence of the basal horny layer, which may be recognised, macroscopically, as horny pearls, and may be shelled out.

While the hyperkeratosis thus predominates over the acanthosis, and the products of the former take the place of the latter, the prickle layer is further affected by a degenerative process, more or less widespread. Where the inter-epithelial spaces are much dilated, we note that the prickles of adjacent epithelial cells are here and there lost, that the cells have become more rounded, homogeneous and cloudy, and take up basic colours less, and acid ones more. Finally, the staining capacity of the nuclei is lost, and the epithelial cells are converted into a homogeneous colloid mass. Such epithelial masses are found, singly or in groups, very early in the prickle layer, later, in the centre of the papule, great stretches of the prickle layer are thus affected. But in older papules these colloid masses and clumps always appear at the cutis margin, and, with the withdrawal of the ridges out of the cutis, inside it also.

The most characteristic epithelial changes consist then in an initial acanthosis, which later gives place to epithelial atrophy, in a persistent hyperkeratosis, which leads to the formation of varied horny structures,

and—in contrast to special firmness and dryness of the surface—to a permanent inter-cellular œdema, and a wide-spread colloid degeneration of the prickle layer. We see that there exists in the latter a striking contrast, and, generally in all these epithelial changes, a remarkable resemblance to the epithelial changes in Ulerythema centrifugum.

The cutis shows a dense collection of cells in the papillary body, from the sub-papillary vessels, outwards to the epithelial margins. This is very characteristic of Lichen, firstly, in the sharp under margin from the healthy cutis, then in the minuteness and regular, dense packing of the cells. We never see among them the formation of plasma cells or of larger spindle cells, with several nuclei or processes. They are consequently regarded by the majority of authors, following the present-day tendency, as leucocytes, but without sufficient foundation. The fact that the neighbouring lymph spaces of the epithelium are wide open and nevertheless contain in general only a moderate number of leucocytes, should make us cautious in this assumption. The cells have moderately large, simple nuclei, and very little protoplasm, while a few scattered leucocytes show a distinct small border of protoplasm and invariably a divided trifoliate nucleus. This infiltration, consisting in the main of stationary connective tissue cells, extends a certain distance in all directions, from the lenticular areas underneath the epidermis, in lines along the blood vessels, through the cutis, without usually reaching the hypoderm. One cannot then always distinguish—as in the syphilides—individual vascular cones, which show, all over, the proliferative irritation. But the cellular proliferation of the cutis is limited—as in the parakeratoses—in general to the epithelial margin, and slowly extends from here, in layers, downwards, after processes have extended at the periphery along all the blood vessels. In most forms of Lichen, the zone of sub-epithelial infiltration only forms a small band, which surrounds the coarser ridges like a shell, and extends into the papillæ, completely filling them. Therefore the papillæ undergo club-like or pear-shaped swelling, and compress the epithelial ridges almost to nothing. This appearance of a group of pear-shaped, swollen papillæ, infiltrated by closely-packed, small cells, which run together under the papillæ to form a band, sharply margined from the cutis, is as characteristic of Lichen as the horny plugs already described.

There is always added to the cell proliferation an œdema of the papillary body, which increases from below upwards. At the surface of the papillary body, it separates the collagenous tissue into wide spaces, which are in direct connection with the gaping epithelial spaces. The œdema aids in the club-shaped swelling of the papillæ, but chiefly rarefies the sub-papillary marginal streaks, and favours in many places the loosening of the epithelium from the cutis.

On the cutis, the œdema has an influence analogous to that of the œdema and the hyperkeratosis on the prickle layer; the former gradually disappears, partly by resorption, partly by hyalin degeneration and sclerosis. The resorption is first noted at the most superficial part of the cellular infiltration; in place of the cells, there appear wide lymph spaces, and partly by the formation of lakes of lymph between the epithelium and the cutis, the former is, in small sections, completely detached from the latter. This solution is present in higher degree when the adjacent collagenous tissue is partly hyalin, alongside the colloid epithelium. The hyalin degeneration of the cutis affects also the superficial capillaries of the skin, which may now and again swell up to the thickness of arterial twigs, with loss of their cell contours, and finally also of the nuclei of their endo- and perithelium. In such parts of the disease the cellular infiltration has distinctly receded, and given place to a homogeneous sclerotic change of the connective tissue, and an infiltration of pigment. This conclusion of the process, when the hyperkeratosis of the atrophic epithelium has disappeared, makes itself clinically evident in a scar-like depression of the surface.

The coil glands show, almost invariably, a passive dilatation of the lumen, down to the lower end, which now and again leads to cyst formation. They, as well as the ducts, are surrounded by proliferated connective tissue cells; the rest of the cutis at their lower end is completely free from cellular infiltration. The gland cells appear partly distended and faintly stained, partly small and deeply stained, and a glassy or granular mass is separated in the irregular-looking lumen. In other places the gland tube is simply dilated, with diminution of the epithelium, which is then, often, towards the lumen, as normally in the duct, covered with a sort of membrane; it has evidently become functionless. The sweat pore is almost always plugged, partly by the proliferation of the epithelium of the ducts, which begins as far down as the papillary body, partly by the formation of horny clumps (horny pearls), during its course through the horny layer. Through the falling out of the latter there developes a sort of central dimple, especially in Lichen obtusus.

These histological symptoms, which are more or less evident in all forms of Lichen, are quite sufficient to explain the clinical characters. The **livid, bluish-red colour** is the more pronounced the less the papules reach, at the commencement, over the level of the skin; it is due to the thick cellular layer (thickened epithelium and compact cellular infiltration of the cutis), which lies, like a dense opaque medium, over the dilated capillaries. In contrast to syphilis and lupus, the pressure of the diascope does not show any brownish nodes, for every

characteristic plasmoma is absent. The dark brown or black colour of older papules is brought about by the subsequent pigmentation.

The **burnish** of all the non-scaly papules depends on the stretching of the horny layer, and this on the abnormal pressure, under which they stand during their whole development. There is, at first, along with the epithelial growth, an *abnormal density of the horny layer*, which does not permit of desquamation. If the acanthosis give place to atrophy of the prickle layer, the space which developes is occupied by the swollen papillæ, which press on the epithelium, so that the horny layer, without yielding, always remains stretched to its maximum. On the thickness of the epithelium, and especially of the granular layer, depends whether the papule is shiny-red or has a mother-of-pearl shimmer. In the latter case the waxy burnish resembles that of Epithelioma contagiosum, or still more that of the commencing Rodent ulcer, where the horny layer is also excessively stretched by a thick epithelial cushion. From the *absence of the scales*, and the *burnish*, which both point to an *abnormal firmness of the horny layer*, the very smallest Lichen papule may be distinguished from one of Psoriasis or Seborrhœic eczema, of the same age.

The **dryness** of the Lichen papule and the absence of a tendency to the formation of vesicles, in spite of the inter-spinal œdema, depends also on the firmness and power of resistance, which the epithelium of the papule possesses, from the commencement. In spite of saturation with an excessive amount of lymph, in spite of the non-replacement of young cells, the atrophic prickle layer never undergoes reticular, but only colloid metamorphosis. I do not think I go wrong in recognising in this resistance of the prickle cells, in the resistance of the horny layer to desquamation, and in the persistent hyperkeratosis of the papules, a uniform fundamental quality, which the Lichen process gives to the epithelium, and owing to which it long resists degenerative influences. These, on the contrary, are very soon evident, even at the height of the papule (as in Ulerythema centrifugum), in the uppermost layers of the cutis, in that the inflammatory irritant only leads to rapid cell proliferation and to œdema, but not to increase of the protoplasm of the cells. The latter, as well as the collagenous tissue, and even the vessel walls, undergo a slow stiffening, so far as they have not previously been absorbed.

I. *Simple Elementary Forms.*

1. *Polygonal Papule.*

This appears most typically on the wrist and glans penis, in the form of miliary and sub-miliary, rapidly appearing groups of sharply margined papules. The most characteristic feature is the *straight lined* (triangular to pentagonal)

edging of the papule, a quite exceptional appearance in skin diseases. Ordinary eruptions, be they infectious centres of the epidermis, vascular cones, or nerve areas of the cutis, are so formed, that only round, oval, or polycyclical forms can develope. The straight-lined margins can then only be explained by pre-existing straight lines, and these are the well-known epidermic furrows. But as this border is respected by the papular swelling, it is clear that the swelling must chiefly affect only these elements, for which the epidermic furrows normally form margins, viz., the papillæ.

As a fact, the polygonal papules correspond to a region of ten to twenty closely-arranged papillæ, which are distinctly elevated above the neighbouring papillæ, and are separated from them by an a-papillary furrow.

If the epidermis be removed, the appearance of the papillæ shows this very clearly; they remind one of the fungiform papillæ on the smooth surface of the tongue. The marginal a-papillary furrow corresponds to the broader epithelial ridge, corresponding to that epidermic furrow, which surrounds the polygonal papule on all sides. Frequently, in this swelling, the isolation of many papules is lost, in that they run together at the base, so that only their heads project, and indicate the number of the original papillæ. Now and again the swelling goes on to the development of a connected cushion, from which the epithelial ridges, which were at first only diminished, are completely withdrawn.

The proliferation of the prickle layer, above this papillary region, does not tend to be very great; sometimes it is altogether absent, and the swelling, which is always present, is then solely to be ascribed to a moderate degree of parenchymatous swelling of the epithelium, and to the dilatation of the lymph canal system. The greater the swelling of the papillæ, the smaller do the inter-papillary ridges become; the cross section of a papule shows only remains of thin epithelial pillars, which are connected, like arches, over the papillæ. Finally, the prickle layer is marked off from the papillary cushion below, as a uniform super-papillary pad. More detailed examination certainly shows, here and there, at the seat of previous epithelial ridges, colloid epithelial cells, which it is difficult to see, and which, on retraction of the epithelial ridges, have remained adherent to the swollen papillary body. (Fig. 14.)

The hyperkeratosis is, from the commencement, equally developed over the papule; the granular layer is markedly thickened, as is the horny layer, especially the basal horny layer, which is stained black by osmium. There was no special relation to the sweat pores and follicles. If these, as is often the case, are enclosed in the papules, their outlets (sweat pores, follicle necks), sometimes take part in the acanthosis and hyperkeratosis, but not invariably, and so long as the

polygonal papule remains as such, there is no development of horny plugs. As in the further course, the epithelial growth again gets the upper hand, and the hyperkeratosis leads to horny pearls and horny scales, the character of the polygonal papule also disappears, and, by peripheral extension, or more often by coalescence, it passes into plane, verrucous or other combined coarser forms. The surface of the polygonal papule is always smooth, the colour a simple bluish-red.

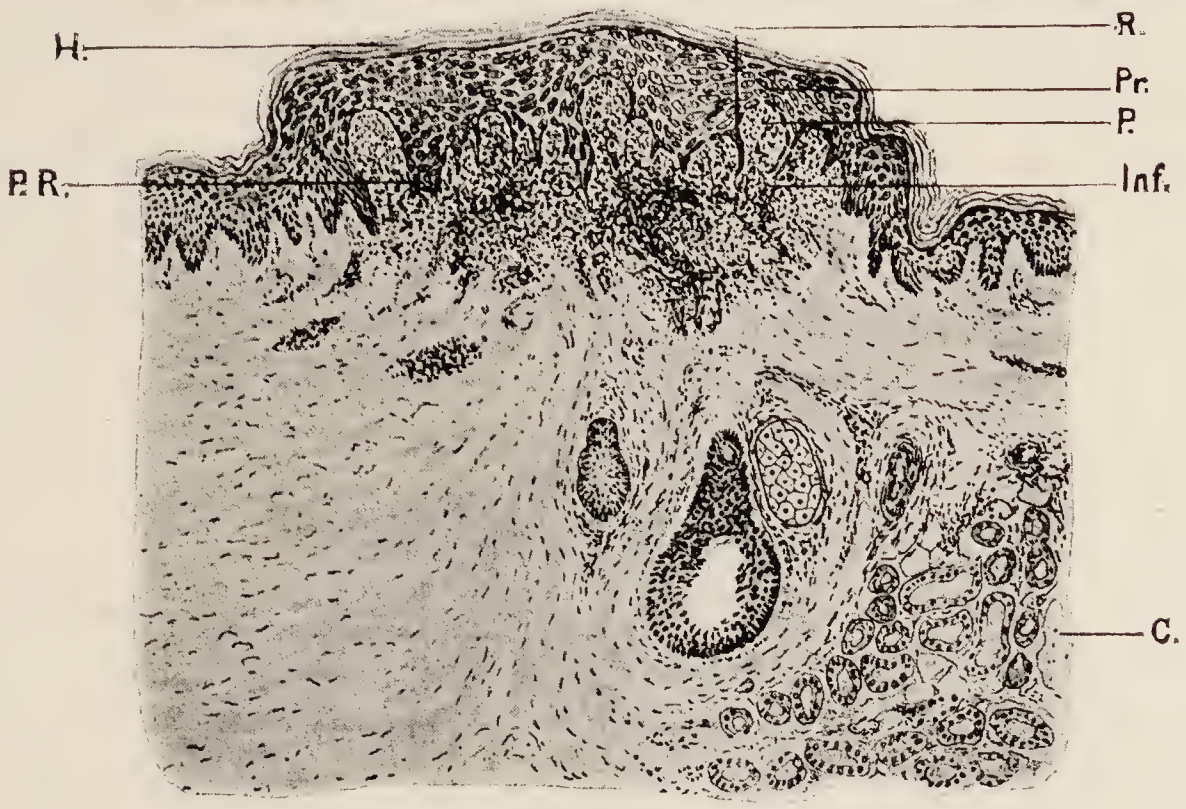

FIG. 14.—Lichen. Polygonal papule.

Inf. Small celled infiltration of the papillary body.
P. Round swollen papilla, filled with infiltration.
R. Very much thinned and pointed epithelial ridges arching over the infiltration.
Pr. Prickle cells horizontally enlarged.
H. Thickened and stretched horny layer of the basal type.
P.R. Epithelial ridges thickened by secondary growth.
C. Coil glands, dilated, the epithelia of some swollen.

2. *Obtuse Papule.*

The obtuse papule is now and again mingled with other forms, but appears usually—and in typical cases always—as the predominating form of the eruption, especially in children. This circumstance points to the fact, that the specific poison, in this case, follows a special mode of invasion. And in fact a sweat pore is found in the centre of the papules in typical cases, which is itself very much altered, and leads to an altered coil gland.

Further, it is characteristic of the obtuse papule, that it is not limited by the epidermic furrows, and therefore, like all other eruptions, it possesses a roundish, almost a circular form.

Consequently the papillary swelling is not so predominant in it as in the polygonal papule, but it extends to a much larger area of skin, since, from the centre towards the border, it diminishes, first very little, then more rapidly. On the other hand, acanthosis is here more

developed at the commencement, and this naturally interferes with any sudden alteration in height at the border of the papule, for it also, towards the periphery, very gradually diminishes.

The granular and horny layer, both much thickened, run, slightly projecting, smoothly over the whole papule. The sweat pore at the summit of the papule is filled by a concentrically sheathed, spirally twisted, or later, globular irregular horny mass; where this horny pearl falls out, one sees clinically a hole, as if made with a pin.

The prickle layer shows a large amount of œdema, and colloid transformation of single epithelial cells and groups of them. Corresponding to the moderate swelling of the papillæ, we find regular, though much reduced, epithelial ridges penetrating the cutis, which, on cross sections, have the form of little pointed triangles. The cellular infiltration underneath the epidermis is also equally well marked. It has an almost perfect lenticular form, and is penetrated by wide blood vessels and lymph spaces. But the usual secondary epithelial growth, the natural result of the hyperkeratosis, as well as the later sclerosis, is not, in this form, prominent.

A further characteristic of the obtuse papule is the invariable, but not always so definitely pronounced change in the coil gland. This is mainly to be regarded as a *cystic degeneration*, a result of the plugging of the sweat pore, which takes place in the horny layer. But we must also admit inflammatory changes, on account of the proliferation of the connective tissue cells surrounding the coil. The lumen of the duct is dilated, that of the coil still more so. The epithelium of certain coils is flattened, and clothed with a sort of cuticle, a thickened inner sheath of the cell, which makes duct and gland epithelium look very similar. A few loops contain enlarged epithelial cells, in which the protoplasm is swollen, and the perinuclear zone dilated. The lumina of such loops sometimes show glassy or granular masses, which are derived from the epithelium. The significance of this I must leave unexplained.

3. *Follicular Papule.*

As the obtuse papule shows a constant relation to a sweat pore, so does the follicular to a hair follicle. These also appear, combined with other papules, sometimes independently, sometimes as parts of combined forms, especially of the corneal and verrucous. In the latter case they are represented by horny taps, penetrating more or less deeply into the follicle. But the follicular papules are also occasionally pure; they form, in Lichen neuroticus, the "red goose skin," which, at first alone, later, on the borders of diffuse erythrodermia, characterises this affection.

At the summit of the follicular papule opens the mouth of a lanugo hair follicle, with widely dilated neck, filled with concentrically-

sheathed horny wedges. In many of the necks the development of the horny layer is so great, that the section resembles, not the ordinary filter, as it lies in a funnel, but a folded Swedish one. Along with the horny layer, the granular is also thrown into folds. The surrounding horny layer of the surface epithelium is also thicker and more dense, and either passes, as a firm covering, over the exit of the follicle, or is penetrated by the hair and its sheaths. In the former case the hair is retained, as in Hyperkeratosis supra-follicularis (so-called Lichen pilaris) and lies in the neck of the follicle, bent up or rolled together; the papule then appears at the apex whitish, but smooth. In other cases there reaches, from the dilated follicle, a concentrically-sheathed horny plug, surrounded by a fringe of thickened and folded horny layer; the papule in this case carries a firmly-adherent horny scale.

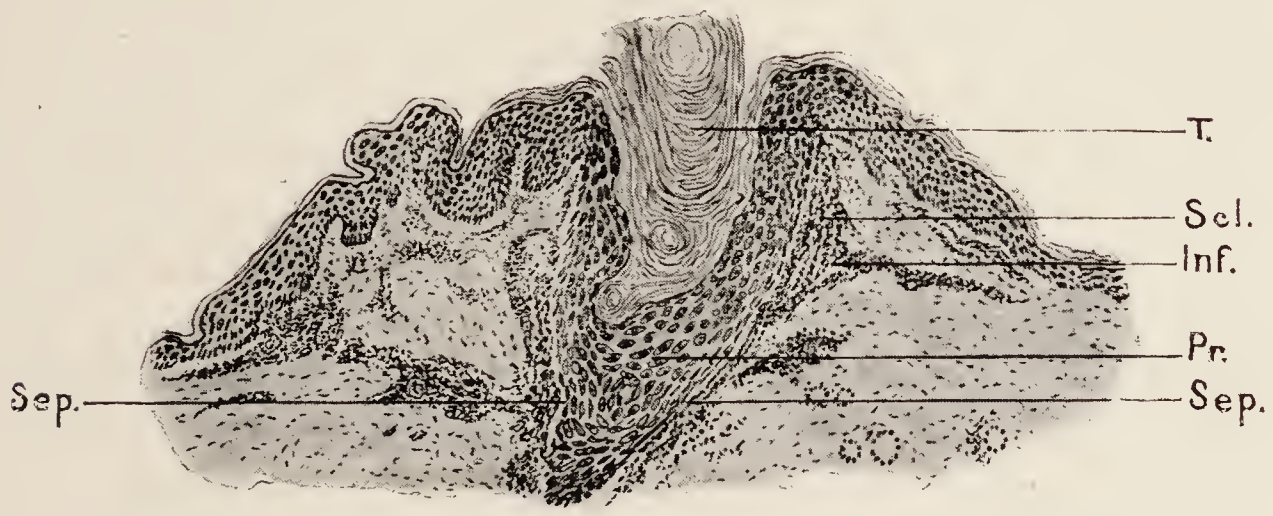

FIG. 15.—Lichen. Follicular papule.

T. Wedge-formed Epithelial plug, continuous with the horny mass around the hair.
Inf. Small-celled infiltration around the follicle.
Pr. Widened prickle cells of the prickle layer of the hair follicle, less well stained outwards.
Sep. Separation of the follicular epithelium from the hair follicle, whose collagenous tissue at *Scl.* is sclerotic and tends to fissure.

The papillæ, lying directly at the exit of the hair, are, at the commencement, distinctly swollen and their blood vessels are dilated, so that, at this period, the conical projection of the spot is partly to be ascribed to this swelling, and partly to the thickening of the horny layer and the pressure of the horny plug. After longer duration, we find, on the contrary, the prickle layer of the surface, round about the hair follicle, distinctly and irregularly proliferated. A section will sometimes show, on one side of the hair follicle, much swollen papillæ, with the suggestion of young epithelial ridges between, on the other, the papillary body, pressed down by a thick cushion of prickle cells to its previous level or beneath it, and the border line once more flat.

During this new epithelial proliferation, the horny layer of the surface and of the follicle neck is retained, or, at most, undergoes slow, insensible desquamation. The result is a great widening of the

granular layer, especially where the horny layer dips downwards. At this period the process only rarely remains limited to the immediate neighbourhood of the follicle, and consequently the character of the pure follicular papule is lost.

These characters of the follicular papule are not very satisfactory in distinguishing it sharply and definitely from the totally different Pityriasis rubra pilaris, with which, under the names Lichen ruber (Hebra), or Lichen accuminatus (Kaposi), it was so long confused. Both forms of papules show hyperkeratosis supra-follicularis and follicularis, deformities of the hair, acanthosis, and papillary swelling. The differences of the horny substance and of cornification, which are here present, are too subtle to enable us to make the differential diagnosis off-hand. But that is both possible and easy if we consider the œdema, culminating at the epithelial margin, the colloid degeneration of the epithelium, the hyalin change in the blood vessels, and the sclerosis of the connective tissue, which are as well developed in the follicular papule, as in other forms of Lichen. The addition here is especially the sclerosis of the upper part of the follicle. This leads, in many places, to loosening of the epithelium of the neck from the walls, just like that of the surface from the papillary body, and it is sometimes completely removed in cutting the section. The upper segment of follicular epithelium also participates in the inter-spinal œdema and the colloid change of certain epithelial cells.

This œdema, and the retrogressive processes depending on it, are not found in Pityriasis rubra pilaris, but we meet there other acute processes in the follicular epithelium (see there for more thorough differential diagnosis). The tissue of the hair follicle itself, its vessels, and the peri-follicular connective tissue show, since here, as there, a rich cellular infiltration exists, a certain resemblance. But in the lichen papule the infiltration is more limited to the upper part of the follicle, and consists of the equal small cells described, in œdematous, collagenous tissue, while the cellular infiltration of the pityriasis papule affects equally the whole follicle, often appearing, for preference, in its under part, and is composed of different kinds of cells (see again Pityriasis rubra pilaris).

The lanugo hairs themselves show no changes, apart from the initial rolling and bending referred to. They are eliminated with the throwing off of the horny plug, and, so long as the lichen process exists, are not again formed. The sebaceous glands also are unchanged and tend to atrophy, which, it appears, in long-standing cases, affects them all. But the arrector muscles are always very evident, are very broad, and frequently surrounded by cellular infiltration.

4. *Plane Papule.*

This form in independent development is, by preference, limited to the extremities and the head, but, combined with other forms, is found in almost every case of extensive Lichen. These flat, scarcely elevated, shiny papules, of the size of a lentil to a pea, usually show a tendency to increase peripherally, and then form shilling to half-crown-sized patches, often depressed in the centre. They arise from the confluence of polygonal papules, are developed from the general erythrodermia in Lichen neuroticus, and on their side supply the basis for the development of the corneal and atrophic papules, which are only varieties of the plane.

Histologically, the plane papules are characterised by the absence of marked papillary swelling. There is therefore, very early, a smoothing out of the papillary body. A flat lenticular or band-shaped cellular infiltration of the cutis margins the thickened plate of the prickle layer. At the most there are fine arch-like remains of the original ridge system entering the cutis. Œdema of the prickle layer, colloid metamorphosis of the epithelium, and sclerosis of the connective tissue margin, beneath the epithelium, are typically developed. But the dilatation of the blood vessels and the formation of the cellular infiltration are here less. Both the sweat pores and the follicular entrances, in relation to the papule, take part in the epithelial growth, and the hyperkeratosis indicates itself by spirally-twisted and wedge-shaped horny taps.

As a whole, the plane form is that of lesser reaction of the cutis and greater of the epithelium. This is especially seen in the extension of the process, where the epithelial growth, with consequent hyperkeratosis, leads to the profuse development of all those horny structures, which are characteristic of Lichen. In this connection it is noteworthy that the acanthosis never extends equally, not even in one particular spot. One finds, close by one another, deep down in the cutis, broad taps and ridges with secondary epithelial processes, and quite unproductive parts of the prickle layer, atrophic and partly colloid. There also exists a slow but constant alternation between the active penetration of the epithelium and its passive retreat before the irregularly swelling papillary body; we find sometimes deeply-stained, convex, mitotic, epithelial processes extending downwards, and others again, hardly stained, concavely excavated, degenerating, and in process of withdrawal out of the cutis.

The hyperkeratosis is also irregularly extended over the surface of the papule. One finds the largest horny enclosures in relation to the formation of all broad taps and ridges. In them the horny layer, like the scales of an onion, descends, forming, inside the taps, semi-

spherical, inside the ridges, semi-cylindrical horny bodies, which are regularly bordered by a broad granular layer. The horny plugs of the sweat pores and follicular entrances are now also converted into more spherical structures. All these bodies inside the older papules become, from pressure, pretty homogeneous, and are isolated from the rest of the horny layer; they form the "milium"-like horny pearls, which may be shelled out with a blunt instrument. Further, in correspondence to the invariably irregular character of these epithelial changes, we often find coil ducts and hair follicles, opening inside or

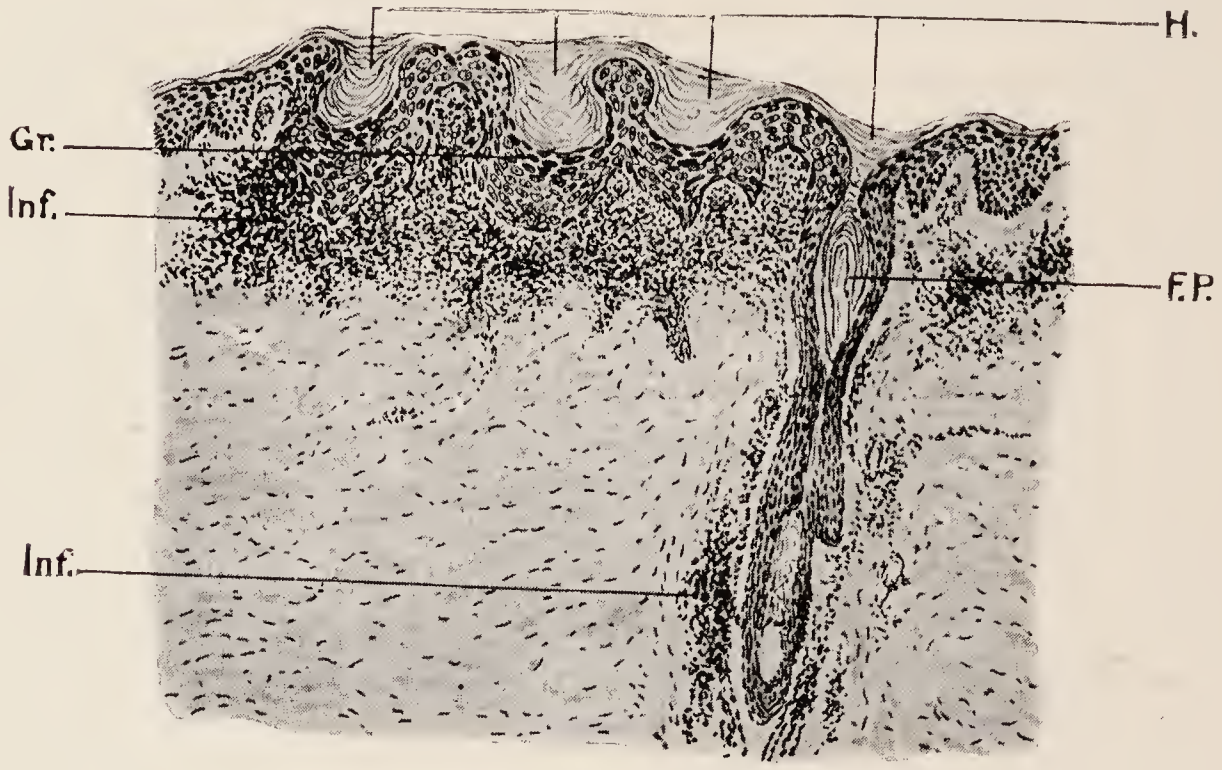

FIG. 16.—Lichen. Plane papule.

Inf. Cellular infiltration of the papillary body and hair follicle.
H. Thickened horny layer, which sinks down and forms three free and one follicular horny pearl, *F.P.*
Gr. Granular layer which, at the base of the horny pearl, is thickened to three or four rows.

immediately in the neighbourhood of the papule, completely free from acanthosis and hyperkeratosis.

The *corneal* type (Lichen corné: Vidal) is only the extension of the plane papule, in the direction of epithelial production. Constant acanthosis makes the appearance of the epithelial margin once more uniform, since the swelling of the papillary body gradually disappears, and the prickle layer extends more and more to a thick uniform cushion. Above this, the granular and horny layers are again horizontally arranged. The horny pearls, produced by the previous wavy bending, are no more formed, but the very firm, non-scaling horny layers run together to a resistant horny plate, of the structure of the basal horny layer. Where, on section of such a papule, several of these cushions are present, separated by unproductive areas, there are also found, on the surface, several separated horny platelets. In such cases the surface of the papule is, clinically, beset with single

shields, nodules or spikes. Where, on the contrary, the whole prickle layer has run together to a uniform, broad epithelial cushion, the horny covering forms a compact callosity, something like a corn, often penetrating in the centre below the level of the skin.

The changes of the cutis are the same as in the other forms. The cellular infiltration is as little developed in Lichen corneus, as in Lichen planus in general. In the secondary epithelial growth it nestles around all the ingrowing taps and ridges, and has a very irregular distribution, but it always remains mainly sub-epithelial; in the final flattening of the prickle layer it attains once more the form of a flat shell. In cases of very long standing, the cutis inside the infiltrated zone is, in the plane, and possibly still more in the corneal form, deeply pigmented. Considering the great pigmentation of the cutis, the slight pigmentation of the basal prickle layers is remarkable, and this seems to me to depend on the œdema, the diminished nutrition, and the tendency of this layer to colloid degeneration.

A very rare variety of the plane elementary form, is the *atrophic* (Lichen atrophique: Hallopeau). Darier has published a description of it, which, in almost all points, exactly corresponds with that of the plane papule. There were found, in all the sweat pores, horny pearls, and the ends of the coil duct were not only affected with acanthosis, but with hyperkeratosis—a deep penetration of cornification into the duct, which has certainly never previously been seen. The horny and granular layers were widened, the prickle layer atrophic and partly colloid, and the hair follicles normal. The peri-vascular cellular infiltration was distinct, but very slight, and the cutis was sclerotic, not only at its epithelial border, but in its whole thickness. On this latter point, Darier rightly lays most weight. We have, therefore, to regard the atrophic papule as a plane one, in which the sclerosis of the cutis has attained such dimensions, that the epithelial proliferation is interfered with, and the horny production does not go beyond the formation of horny pearls. In contrast to the ordinary plane and to the corneal papule, the atrophic shows a lighter colour and very little pigment, which may very well be due to the excess of connective tissue sclerosis.

II. *Synanthems.*

5. *Ring-formed Papule.*

The anatomy of the ring-formed, accidental developments of the plane papule (papula gyrata), which are now and again observed, especially on the leg, has still to be investigated. The clinical characters indicate that one would meet, in the healing centre, remnants

of the lichen process, while the process was extending, at the periphery, with acanthosis and cellular infiltration.

Of the true, *substantial*, *annular* Lichen I have had the opportunity of examining one regionally limited to the scrotum, and one universal.

The spot, the size of a pea, rising from the greyish-blue pigmented scrotal skin, and presenting a fine mother-of-pearl glaze and a rolled edge, showed a characteristic structure. In the centre, at the level of the surrounding skin, the ridge net is only slightly hypertrophic, and the papillæ slightly but definitely swollen; both papillæ and ridges slant somewhat obliquely from both sides, towards the centre. In contrast to the centre, which shows little abnormality, the two borders of the eruption are indicated by enormously increased ridges, which, on section, as two deeply penetrating epithelial taps of club-like form, penetrate the thin scrotal skin, and laterally limit the affection. The granular and horny layers over them are only moderately widened, and these marginal parts are elevated like ridges from the subcutaneous tissue, not so much outwards as inwards. But one readily understands, clinically, that the deep lateral epithelial growths must elevate a very narrow portion of the horny layer, and stretch it to a maximum, and this explains the mother-of-pearl appearance of the ridge.

These lateral rings are surrounded, on all sides, by a thin shell of cellular infiltration, which mainly consists of the small uniform connective tissue cells of lichenous infiltration, and, in a much lesser degree, of leucocytes. A number of leucocytes invades from here the large marginal ridges. The papillary body in the centre shows only a very slight cellular infiltration of the papillæ, and no œdema round the vessels, but a pretty marked pigmentation, which must here be ascribed to the general scrotal pigment, as it was also found round the papule. The blood vessels are not notably dilated.

Very remarkable in this lichen is the absence of colloid epithelium, hyalin vascular metamorphosis, and the sclerotic changes of the collagenous tissue, those regressive changes which usually, at least in moderate degree, accompany all forms of lichen, and contribute much to their character. The single suggestion and forerunner of this regressive metamorphosis is seen in the dilatation of the lymph spaces in the prickle layer; here and there, we also see the prickles of a few epithelial cells rounded and absorbed. And these œdematous changes of the epithelium are limited to the actively growing marginal ridge. In view of this, it is all the more necessary to point out those alterations, which are present in Lichen annularis, and characterise it as true Lichen. These are: parenchymatous swelling of the epithelium, inter-spinal œdema, epithelial growth, widening of the granular and

horny layers, and compression of the latter, without any trace of scaling, and finally, equally distributed small cell infiltration, in the form of a purely sub-epithelial zone, nestling up to the epithelium. All these symptoms, which are found at the marginal ridge, make that part of the affection so lichenous that one would scarcely think of any other affection.

While the true lichen nature is thus as evident on anatomical examination as on clinical, the absence of colloid and sclerotic changes, as well as of hyperkeratosis with its horny pearls, points to the comparatively fleeting and superficial nature of this form. For this also speaks the serpiginous extension, and the ring form as such, which, although not absolutely foreign to lichen, is by no means so characteristic of it, as of most other dry cutaneous catarrhs.

I have several spots from a very remarkable universal case of Lichen annularis. In this, also, there is a distinct difference between the centre and the marginal ridges of the spots, but less than in the case just described. Then the papillæ in the centre are all of them more or less swollen, the ridge system is reduced to a series of arches, and the thickened prickle layer reduced to a horizontal supra-papillary cushion. The cellular infiltration and the œdema of the epithelial border is moderately developed, and here and there are signs of degeneration. Consequently we find, as a whole, the evidence of a past, and partly retrograde lichenous affection. On the other hand, at both margins, the lichen process is, to the extent of three or four papillæ, fully developed. The prickle layer is here doubled, indented by club-like papillæ, and surrounded by a very broad shell of infiltration; the granular and horny layers are increased. The œdema is extensive, the degeneration processes are, at least, suggested. The ridge-like elevation in this annular form is therefore not to be ascribed mainly to the marginal epithelial growth, but equally to the thickening of all the strata and of the infiltrated papillary body. The whole appearance corresponds to the ordinary one of the polygonal or obtuse papule, except for the contrast between margin and centre.

6. *Lichen Patches.**

Lichen patches are formed from the confluence of groups of polygonal or plane spots. They undergo, like the latter, the corneal or verrucous, and, now and again, the atrophic transformation. Their sign-manual is "en gros," like that of the plane papules "en detail"—the irregularity. But as a whole they tend to hyperkeratosis. They

* I have used the English "patch," as best expressing the German "scheibe."—N. W.

are either smooth, and then form preferentially horny pearls in the ridges and sweat pores, or they form callosities and horny shields. Enclosed hair follicles have the same appearance as the isolated follicular papules. All the elementary, anatomical changes described, may be found in one single patch ; in parts, there is active epithelial growth, which, however, never shows the completely irregular form of a-typical growth (as in lupus), but is always in inverse relation to a cellular infiltration, close around the epithelium, by which it is enclosed, or indented in an arch-like manner.

One often sees obtuse and plain papules, arranged in rows like a string of beads, over the larger cutaneous veins ; these show a definite

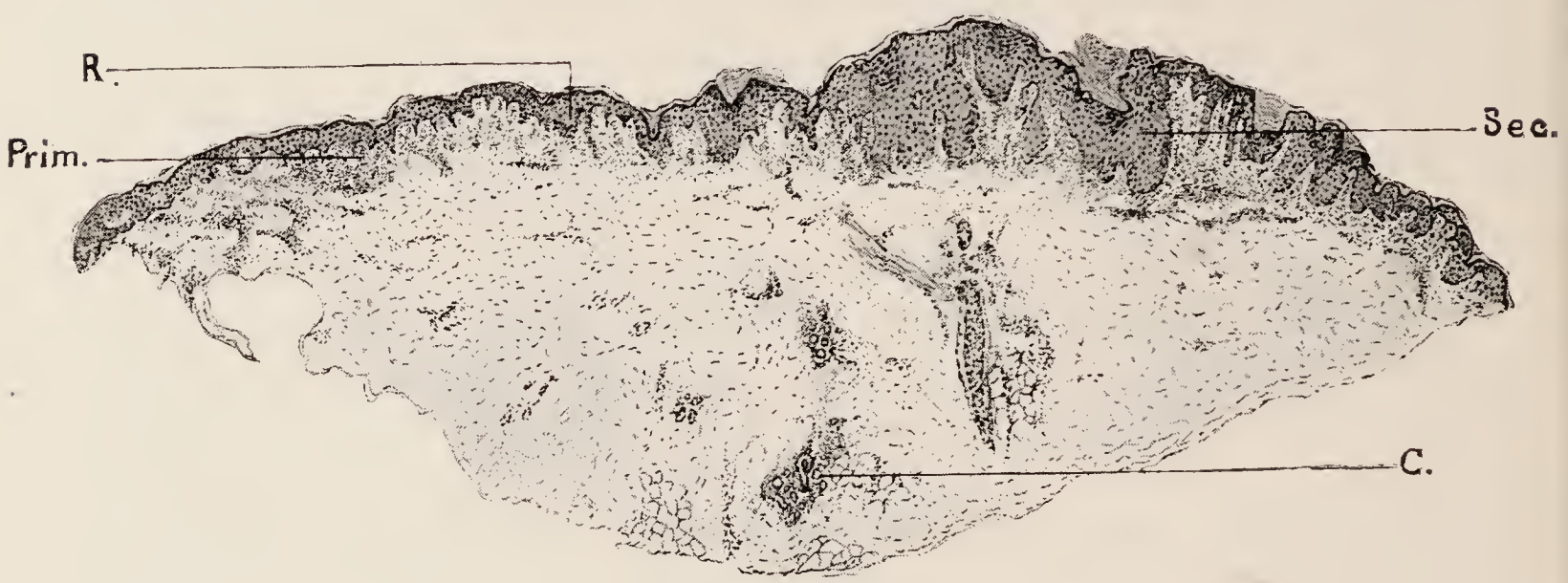

FIG. 17.—Patchy Lichen.

Prim. Primary stage of lichenous change, with wedge-shaped thickening of the cellularly-infiltrated papillæ; underneath, sharply-margined infiltration of the papillary body, swelling of the super-papillary prickle layer, reduction of the inter-papillary ridges to arched, pointed remnants, complete obliteration of some ridges, *R.*, and tension of the thickened, non-scaling horny layer.

Sec. Secondary stage (hypertrophic Lichen), with marked proliferation of the super- and inter-papillary prickle layer, deep penetration of the horny layer to form horny pearls and horny taps, which are surrounded by thickened granular layer.

C. Cystically dilated coil glands.

relation to congestion, but no special synanthem. But Kaposi has described it under the name of the *moniliform* or "*coral bead*" *form of Lichen ruber planus.* There were found widely spread, rosary-like, net-formed, branching lines on the skin, whose lichenous nature Kaposi deduced from true lichen nodules, which were present in great numbers around these cord-like structures. Histological examination was requisite to clear up two things ; first, the lichenous nature of the primary spots, then the actual nature of this unusual development. Unfortunately it did neither. Kaposi found *both the primary and the secondary spots* "to consist of a dense cellular and nuclear infiltration of the sub-papillary (?) layer of the corium, without any trace of organization or structure of connective tissue. There were found only cells, many naked and polymorphous (?) nuclei, biscuit-shaped, half-

moon-shaped, and many cells with the appearance of retrograde metamorphosis, distended, and undergoing cloudy swelling, and a good many giant cells (?). And that tap and feathery-like out-growth of the external root-sheath (?), better seen in Lichen ruber than in any other chronic dermatosis, may here be very well seen."

On the one hand, we lack all positive statements about the very remarkable architectural and structural changes of all the epidermic layers, about any kind of horny bodies, and about the œdema and the sclerosis of the connective tissue, things, which, in such a well-developed true lichen, could hardly have been missed. Instead of this, Kaposi notes a "sub-papillary" cellular infiltration, while it is notorious that the papillary is, in lichen, the most characteristic and often the only one, and further, the presence of "giant cells," which are as foreign to lichen as plasma cells, which usually form their fore-runners. Finally, the follicle epithelium has grown out "like a plume"; this is a very suspicious statement. It was described in the old "Lichen ruber," *i.e.*, in Pityriasis pilaris, Devergie; in what we now call Lichen, Wilson's Lichen planus, these out-growths are not present, but rather a loosening and a degenerative process of the follicular epithelium. Further, it is not easy to understand how Kaposi could have missed, in a true lichen, inside the cellular infiltration, "every trace of connective tissue." Nor can the discovery of "cells undergoing cloudy swelling" (epithelium ?) materially help in this fundamental difference from the true lichen; the histological diagnosis of lichen is confirmed, neither in the primary nor in the secondary spots. Rather, if we regard Kaposi's observations as facts, his examination leads only to a complete disharmony between the clinical diagnosis and the histological structure.

It is to be hoped that this gap will soon be filled, or the true nature of Lichen moniliformis discovered.

7. *Erythrodermia.*

This name, invented by the French school, has been appropriately introduced by v. Düring for that general redness and infiltration of the skin, which, in Lichen neuroticus, gradually developes from the follicular papules and the inter-follicular erythema, and heals with marked pigmentation. In the remarkable epidemic of lichen (1881-1882) in Hamburg, I unfortunately missed the opportunity of excision, and have lately only seen these cases rarely, the last in 1888. But I received from Prof. v. Düring a piece of skin from a patient affected with Lichen neuroticus, which demonstrates well, at least some of the processes under consideration.

The case is shown to be one of true lichen on several sections of this piece, which show small, typical plane papules, and on others in which isolated follicular papules are visible. But in the explanation

of erythrodermia, those places are of importance where appearances of inflammation are to be seen, independent of these developing plane, and older follicular papules. These consist in an increase of the connective tissue cells of the papillary body, as far down as the sub-papillary vascular net. These cells are not so small as those of the sub-epithelial, most characteristic lichenous affection. In a few places, in relation to three or four papillæ, they are already collected into small areas. The prickle layer over these areas is still completely intact, as is the granular layer, but the horny layer is thickened and split into lamellæ. All through the specimen the vessels are more distinct than normal, from increase in the number and size of the perithelial cells, especially the superficial, but also the deeper ones. If we might attribute these appearances, in the neighbourhood of a true, developing lichen papule, which do not tend to develope on otherwise intact skin between lichen papules, to the erythrodermia there found, it would represent a complex of symptoms, composed of dilatation of the vessels, slight perivascular cellular infiltration, and thickening of the horny layer, with a tendency to scaling. While these symptoms are pretty universally spread over the skin, and the follicles are already converted into true lichen papules in the affected areas, in some places the cellular infiltration of the papillary body increases and forms the basis for later plane papules, since probably—this must be decided by later investigation—at these places the characteristic epithelial changes of lichen develope.

If this provisional survey of the histology of Lichen neuroticus is, in the main, right, this form of lichen comes nearest to the parakeratoses; for here alone is there a superficial extension, a tendency to scaling, and therefore a slight permanent anomaly of cornification, of the same nature as is present in the parakeratoses.

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Ichthyosis.

Since many diseases, accompanied by excessive production of horn, of quite different nature, are often grouped together as Ichthyosis,

it is important to make our definition clear, at the commencement. It does not embrace especially the following skin affections:—(1) all so-called "localised ichthyosis," like the *stagnation keratosis* of the under extremities, in Ulcus cruris, Elephantiasis nostras, the *trade keratoses* of the arm, the *keratosis of paralysed limbs* in Tabes, hemiplegia, etc.; (2) the so-called Ichthyosis fœtalis (s. *Hyperkeratosis fœtalis;* (3) the so-called Ichthyosis palmaris (s. *Keratoma palmare et plantare hereditarium et non hereditarium* and other palmar keratodermiæ); (4) all *cutaneous horns,* especially the generalised; (5) the *keratoid nævi,* especially the nævi lineares, with production of horn, which were previously described as nerve nævi or neuropathic nævi; (6) *Hyperkeratosis supra-follicularis* (Lichen pilaris); (7) *Keratoma folliculare, Brooke;* (8) *Keratosis pilaris, Brocq;* (9) *Pityriasis rubra pilaris.*

Ichthyosis is characterised by a collection of horny substance in the form of scales, shields, flat thickenings of the horny layer and spiky protuberances, which always appear symmetrically and *universally,* and like Pityriasis rubra pilaris, affect especially the extensor sides, particularly the *elbows* and *knees,* but in contrast to that, are mostly limited to the trunk and extremities, seldom attack the head and neck, and never appear on the scalp. It is absent at the *contact regions* (axillæ, inguinal regions, and the flexor sides of the elbows and knees), and is always less developed on the flexor sides. The ichthyotic surfaces are distinguished by a marked degree of *dryness, i.e.* by an absence both of fluid and of fat; they tend to plugging of the follicles, but never of the sweat pores (as in Pityriasis rubra pilaris and Lichen) and pass without a sharp margin into the healthy skin. The horny masses have (in contrast to those of Pityriasis rubra pilaris) a tendency to the formation of a *horny colour,* and are mostly greyish-brown, greenish or black. As in Pityriasis rubra pilaris, there exists also in Ichthyosis an *extension of the horny layer,* over-compensating the surface tension, by which a coarse folding and marking of the surface is developed (in distinction to those catarrhs of the skin with typical parakeratosis), while scaling is minimal. Ichthyosis first begins in the second year of life or later, and represents a family tendency; but hereditary, in the strictest sense, it is certainly not; at least there is no proof of it; congenital keratodermiæ are quite of another nature and are seen immediately after birth. Profuse sweating improves ichthyosis; it sometimes heals during acute fever, and it also heals, if appropriately treated sufficiently early. Its usually latent inflammatory symptoms, under unfavourable circumstances develope, and then appears, with *scaling, itching,* and *weeping,* the picture of a cutaneous catarrh with typical

parakeratosis. In certain regions of Asia, Ichthyosis is said to be endemic. This points to the fact that true Ichthyosis, analogous to Pityriasis rubra pilaris, is an infectious hyperkeratosis, tending to parakeratosis, and is equally distinct from the congenital dermatoses and the neuropathic keratodermiæ. It shares with Psoriasis the anhydrosis, the preference for the extensor sides, the transition into moist catarrh and the heredity of disposition.

One usually distinguishes three forms of ichthyosis, which also correspond to grades of intensity; *Ichthyosis nitida, serpentina and hystrix.* This division may also be retained histologically, for the first and mildest form corresponds to the ordinary ichthyosis with predominant hyperkeratosis; the second, rarer, to the addition of acanthosis; and the third, rarest, to the appearance of a circumscribed, excessive, secondary hyperkeratosis. Elementary forms, such as in Lichen and in Pityriasis rubra pilaris, there are not, for the disease appears diffusively from the commencement, and we do not — like many dermatologists — regard so-called Lichen pilaris, a follicular hyperkeratosis, as Ichthyosis. The follicular affection, which is present in Ichthyosis, does not clinically appear independently. The appearance of groups of protuberances, of so-called spikes, is a consequence and not a grouped element of the eruption.

1. *Ichthyosis nitida.*

The less severely the ichthyotic process is developed, the more is it limited to hyperkeratosis as its chief symptom. This is not severe, only, instead of normal insensible scales, there are produced coarse, smooth, flat ones. These are greyish and transparent, or of a dark slaty colour. The surface extension is not yet much developed, consequently there appear fissures which divide larger polygonal scales.

The previous increased tension of the superficial horny layer, from which the scale is formed, is shown by the fact, that the latter is somewhat drawn together, and elevated, at the borders, from the surface beneath. Consequently these scales adhere at the middle, or at one border, and attain the transparent appearance, which makes them like half-separated plates of mica.

Microscopically, the hyperkeratosis in this form shows itself in such a characteristic way, that sections can be recognised as ichthyotic, at the first glance. Since there is no concurrent epithelial growth, the hyperkeratosis holds the field, and stamps a special type on the prickle layer and the papillary body. The thickness of the prickle layer, as a whole, but especially that of the super-papillary, has diminished. The individual size of the prickle cells is thus reduced, even so much, that the epithelium of adult Ichthyotics looks like the epithelium of new-born children or of very old people; the volume of the protoplasm is

more reduced than that of the nuclei. We have consequently to do with a small super-papillary plate and with ridges whose shortening is caused not by diminution in the number, but in the size of the epithelial cells. Further, the form of these ridges is characteristic; they are flattened on the under surface as if indented. However they arise from the super-papillary layer, broad or small, whether they turn from there directly, obliquely, in loops, or bent towards the cutis, they are *attached to it with equally flattened surfaces, which all lie in an almost horizontal level.* This is the simple result of the equally increased pressure of the horny layer, with diminished epithelial resistance inside the intra-papillary prickle layer, *i.e.* with insufficient new formation of epithelium.

FIG. 18.—Ichthyosis nitida.

Sc. Loose scale.
H. Thickened horny layer.
P. Papilla flattened from above.
E.R. Epithelial ridge flattened from below.
C.I. Sub-epithelial inflammatory cellular infiltration.
M. Cutaneous muscles, pretty numerous.
D. Coil duct running between two smooth muscles.
C. Coil glands with dilated lumina.
F. Coarse infolding of the horny layer.
L. Atrophic prickle layer passing directly into the horny layer without any granular layer.

If the hyperkeratosis continues to increase, almost all the super-papillary prickle layer will be finally converted into a horizontal horny layer, so that the uncornified epidermis is formed almost by ridge net alone. This is one of the rare cases in which the name, net (rete, which, rising from a mistaken view of Malpighi, is still wrongly made use of by many authors for uncornified epidermis) has some justification. The horny layer never completely occupies the place of the

super-papillary prickle layer; the heads of the papillæ are always covered with at least one layer of prickle cells. But in these cases the vertical pressure of the horny layer has also an influence on the form of the papillæ, and flattens them out, so *that their surface comes to lie in a straight line.* Here we have, then, both *straight indented ridges and papillæ.* The shortening of these is—corresponding to the exclusively vertical pressure—partly compensated by the *broadening of the ridges and the papillæ,* and this naturally takes place, in view of their atrophic passive relation, where, from the commencement, their resistance is greatest, *i.e.* most ridges acquire a broad base on their surface next the cutis, and a small neck at the horny surface; the papillæ, on the contrary, have a broader head than neck, consequently both structures grip one another, as if dove-tailed.

This deformity of the weakly developed prickle layer and of the papillary body, together with the equally and much thickened horny layer, unmistakably characterises Ichthyosis. In no dry skin catarrh, although in the especially hyperkeratotic Pityriasis rubra pilaris, is the prickle layer so feebly developed, and, along with the papillary body, subjected to such flattening.

The margin of cornification shows very remarkable abnormalities; the *granular layer is everywhere absent* on the surface of the prickle layer, and also inside the ridges, where it is usually very distinct. This absence of kerato-hyalin is not, as is usual in the dry skin catarrh, combined with the retention of the nuclei of the horny layer; the horny cells have no nuclei, and are *strikingly homogeneous.* Nor can the absence of kerato-hyalin be ascribed to an excessive moisture, as in Eczema, Psoriasis, over the papillæ in cutaneous horns, etc., for the whole epidermis is distinguished by abnormal dryness; nor is the comparison with the cornification of the nails any more promising, for although the horny substance of the nail is particularly firm and dry, the nuclei in it are well preserved. We must consequently admit a special form of abnormal cornification, an unusual form of parakeratosis. It is an especially simple form, for the prickle cells pass directly into horny cells, without the formation of secondary bye-products. It would be well that Ichthyosis should be studied, in this connection, by all those investigators who still maintain, in spite of all contradictions, the development of horny substance from kerato-hyalin. The ichthyotic scales are certainly cornified, and yet they develope from cells completely free from kerato-hyalin. I think it most probable that this absence of kerato-hyalin has some connection with the meagre development of the prickle cells; the juicy intermediate zone of the latter is chiefly absent, while the outer layer, with its prickles, and the nucleus in the centre, are well preserved. Now the kerato-hyalin is developed just in this

intermediate zone of the protoplasm (zone of internal fibrillation). In favour of this is the fact, that in Ichthyosis serpentina, where proliferation of the epithelium is accompanied by increase in volume of the cells, kerato-hyalin is once more formed.

In addition to the smallness of the epithelial cells, their close arrangement is striking, and the lymph spaces of the prickle layer are very, very narrow. The basal prickle cells frequently contain much golden yellow pigment, and this appears in Ichthyosis to be especially limited to the epithelium; only the adjacent parts of the papillary body now and again contain some of the same pigment, free or enclosed in cells.

If the action of hyperkeratosis extends, parts of the inter-papillary prickle layer become cornified, and the horny layer sinks into the broad, still persistent ridges. Thus the under margin of the horny layer, which up to now was quite level, presents once more an irregular, wavy surface. When the horny layer desquamates in thick scales, these have on their under surface irregular, nodular protuberances, and are less transparent. In this way, in many cases of Ichthyosis, the prickle layer, except for one or two rows of cells, is completely transformed into horny layer.

The ichthyotic hyperkeratosis also extends into the follicle necks, but it produces no follicular papules, since there is here neither a concurrent swelling of the papillæ (as in Lichen), nor an acanthosis around the follicle entrance (as in Pityriasis rubra pilaris). The production of new horny masses is also very slow in Ichthyosis. Consequently the altered follicle necks lie in the level of the surrounding skin, and are not particularly noticeable. The anomalous cornification is shown in two different forms. Either the exit is widely open and filled by a broad horny plug, which encloses a more or less spirally-twisted lanugo hair; in this case the under part of the follicle is normal, or—and this is very frequent—twisted and bent in different ways. We then find, on sections made in the direction of the hairs, only the upper and under part of the follicle, while the middle lies outside the plane of the section; indeed, we sometimes find three distinct segments of the same follicle in one section. This distortion of the lanugo hair follicles partly depends on the combined pressure of the collagenous tissue (see below), but mainly on the action of the hypertrophic arrector muscles.

In many other cases we find the follicular entrance closed, and the upper part of the hair follicle, or occasionally the whole of it, converted into a hair cyst. These cysts, at the first glance, look like comedones, but they are very different from true comedones. The cysts contain for the most part hairs, only in relatively small amount

horny masses, and these are not arranged in flakes into a firm body of regular formation (see comedo, Acne), but are loose and irregularly mixed with cast hairs. Fat they contain not at all, or in very small amount, they are not in direct connection with the sebaceous glands. Most of these are already atrophied to small rudiments on the still open follicles; on the cystic follicles they are no longer recognisable, and we find neither a head with its marked horny colour, nor the organisms of the comedo. The cysts are surrounded by a thin

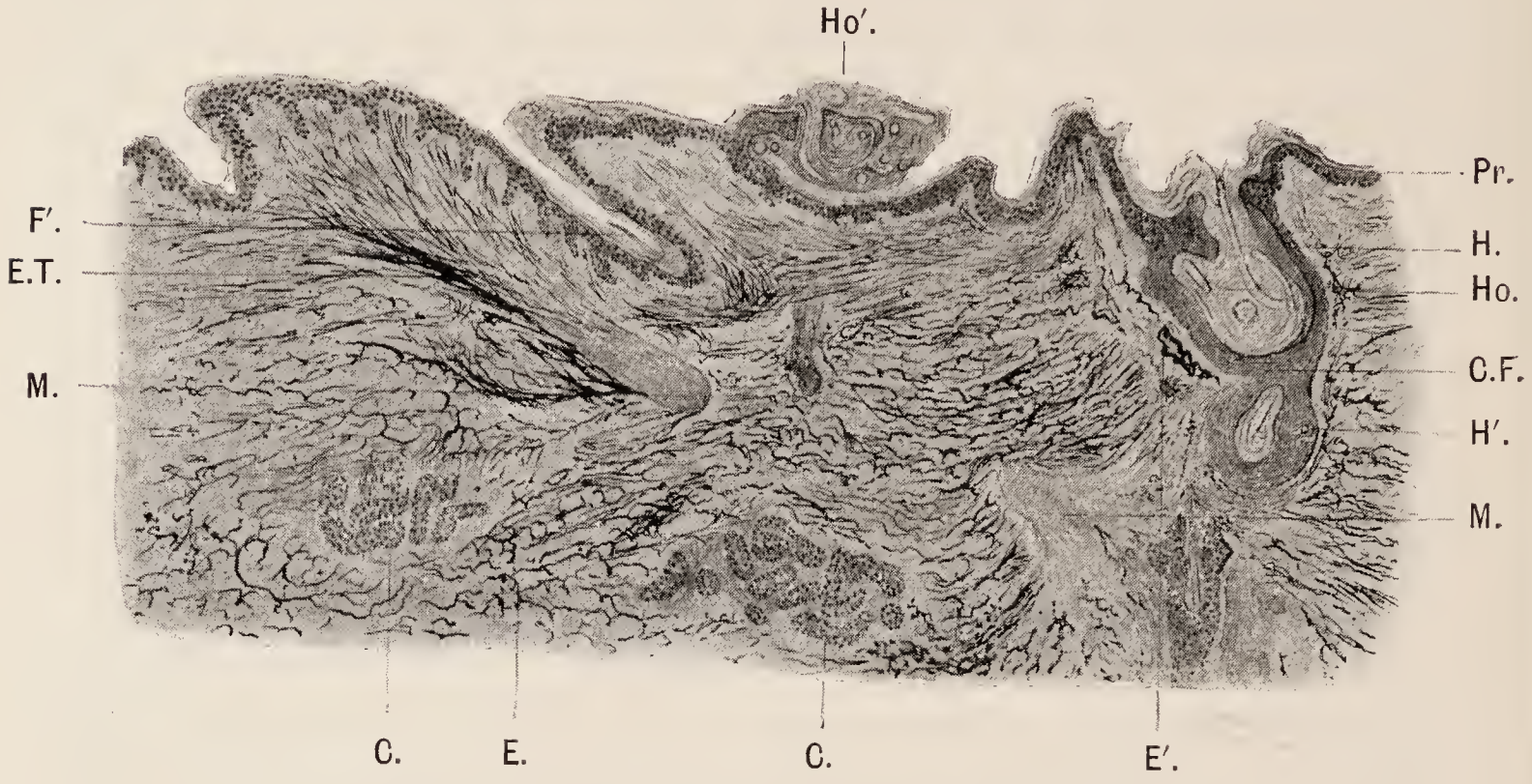

FIG. 19.—Ichthyosis nitida. Acid orcein, Methyl-blue.

C.F. Cystically dilated follicle, with retention of a spiral hair, *H'*.
H'. In it a hair pressed literally into the prickle layer of the follicle.
Ho. Horny cyst in the neck of the follicle.
Ho'. Lateral section of the upper part of a hair-containing horny cyst.
F'. Lateral section of a hair follicle.
M. Muscles, numerous and apparently atrophic.
E.T. Elastic tendon of a hair follicle muscle.
E. Elastin, apparently normal.
E'. Elastin collected in irregular bundles.
C. Coil glands.
Pr. Atrophic prickle layer passing directly into horny layer, without any granular layer.

layer of prickle cells, without any intermediate layer of granular cells. In contrast to the comedo-containing cysts of acne, the cysts of ichthyosis never suppurate.

Often as the follicle necks are altered in ichthyosis, the sweat pores are very rarely so. Of the many cases which I have examined, I have only once found a horny pearl filling a sweat pore (as in lichen), though simple dilatation is certainly often observed. But the changes in the coils are characteristic. Their lumen is regularly dilated, the epithelial cells are voluminous, and all show a broad, glassy, light border, directed towards the lumen, while the nuclei are

as regularly arranged at the outer wall. Thus the loops of the coil very much resemble the undermost parts of the duct, and are only distinguished by the fact that the latter have a double row of epithelium. By the swelling of the epithelium and the dilatation of the lumen, the loops of the coil are, as a whole, much thickened, compress the intertubular connective tissue, approach as nearly as distended loops of intestine, and are often laterally flattened. There is no question, that this very characteristic change of the coils, which has as yet been constantly found only by me, has a definite relation to the constant anhydrosis and asteatosis of the surface. In osmium preparations the black fatty granules, which are otherwise regularly found, are absent. A change of the coil epithelium, making them resemble those of the duct, would indeed indicate a diminished activity. Only in one of my ichthyosis cases, are the coils atrophic, and correspond in their size and that of their epithelium completely to the angular prickle cells of the surface—probably a result of the change of the coil glands.

In the changes of the tissue of the cutis, the cellular constituents play only a subordinate rôle. Certainly the papillary body is sometimes more cellular than normal, and the cells are sometimes larger, as are the endo- and perithelia of all the superficial capillaries, and the capillaries of the hair follicles and coil ducts; the perithelia are often increased in number. But there is never a collection of spindle cells, never a formation of plasma cells; one finds very few mast cells, and absolutely no leucocytes. A small collection of ordinary spindle cells sometimes surrounds the hair follicles. If this lesser degree of activity of the cutis cells serves to distinguish Ichthyosis from the other parakeratoses, and also from Pityriasis rubra pilaris, there is, on the other hand, in the constancy of a slight increase of cells, the proof, that a low inflammatory character is to be ascribed to Ichthyosis also, and that it is not simply a thickening of the horny layer.

The collagenous tissue shows more marked changes in cases of longer duration. We then find it regularly thickened, and the lymph spaces correspondingly narrowed. The thickening especially affects the lower parts of the cutis, the region between the coils and the upper fat lobules. There disappear, with the thickening of the closely interlaced collagenous bundles, the fat of the panniculus, the system of lymph spaces, and the elastic net, which accompanies the bundles. The disappearance of fat in favour of collagenous hypertrophy has the same relation to the inactivity of the coil glands as the increase of the panniculus in seborrhœic alopecia has to their hyperactivity.

In the upper part of the cutis the increase of the collagenous tissue is also present, but less distinct. The elastic tissue is here unchanged. But the oblique cutaneous muscles are regularly hypertrophic; their tendon-like processes of elastic fibres are rarely so distinct and well developed as here. In preparations with good collagenous and elastic staining, one sees the alterations which have been caused deep down by the increase of the collagenous tissue, and the muscular tension near the surface of the cutis, and which are chiefly evident in the deformities of the hair follicles, the dimpled retractions of the surface, and the relative positions of coils and follicles. In older persons these changes seem to give place to a general atrophy of the elements of the cutis.

2. *Ichthyosis serpentina, Sauriasis.*

Those more developed cases of ichthyosis are usually called "snake-like," in higher degrees "crocodile-skin-like," where, instead of the partly elevated scales of Ichthyosis nitida, which give the skin a rough, tesselated appearance, a smoother, more coarsely marked, unfissured, and therefore all the thicker armour of scales exists. The resemblance to a serpent's skin, and, when thicker, to the skin of the crocodile, in such cases is apparent, and is further increased by the dark greenish grey or brownish colour.

We would have no ground for retaining this fantastic clinical division were there only a greater development of hyperkeratosis to distinguish one from the other, anatomically. We have already seen the action of that in Ichthyosis nitida; it does not alter the type of the scaling of the horny layer, and only leads to thickening of the scales. But in the higher degrees of Ichthyosis, and in these very ones with more uniform, coarsely marked surfaces, there appears a new histological element, which explains the different appearances and the altered method of scaling, and enables us to replace the very extensive and indefinite clinical definition by a precise anatomical view.

If the ordinary slighter cases of Ichthyosis are distinguished, in addition to the hyperkeratosis, especially by the inactivity of the prickle layer, the reduction of the volume of the cells and the passive deformation of the ridge system, the addition of a greater activity of the prickle cells, and an increase in their volume and number, must have of itself, as its result, a very different arrangement of the surface. As a fact, the characteristic, atrophic, deformed appearance of the ridge system and the papillary body is at once lost, when a normal epithelial growth overcomes the hyperkeratosis. The ridges and the papillæ are rounded off, their constricted necks disappear, and they form, as a whole, once more the well-known wavy line, produced by the alternation of spherical papillæ and cross sections of ridges. With their

flattening also disappears the plane margin between the smooth horny surface on one hand, and the cutis on the other. There is formed once more a super-papillary prickle layer, and, with the increase in the volume of the epithelial cells, a granular layer developes between it and the horny layer. The lymph spaces of the prickle layer become more distinct, broader, and the amount of pigment seems to become less, sooner than in Ichthyosis nitida. This greater activity of the prickle cells has, on the one hand, the result on the horny layer, that its surface extension now better compensates the surface tension, and scaling is consequently reduced to a minimum; on the other hand, horny processes penetrate much deeper into the now thickened prickle layer, and there are developed horny plates and horny pearls in the same way, although in more limited extent, than in Lichen, somewhat analogous to the psoriatiform patches of Pityriasis rubra pilaris.

As is evident, there is thus developed a remarkable resemblance to Pityriasis rubra pilaris, and also to certain parakeratoses, especially to pruriginous eczema. This is not accidental, for the resemblance, in the clinical appearances, especially of extensive sauridermatic Ichthyosis, to wide-spreading dry eczema and pruriginous thickenings of the epidermis (Brocq's lichenification) of the extensor sides is sometimes very striking.

These forms of Ichthyosis, which present a moister prickle layer, richer in protoplasm, are the only ones which, from time to time, with itching, burning and redness, partly throw off their horny layer and appear eczematous. The Vienna school recognise in such cases an "added eczema"; the simpler and more probable clinical explanation is that of a simple increase of the always present, but usually more or less latent, inflammatory condition. The confirmation of this view is obtained by the histological examination of such cases. As a fact, there are, actually, in relation to the acute inflammatory changes, the formation of crusts, &c., many evident differences from eczema. I have several crusted papules from an exquisite case of sauridermatic, universal Ichthyosis in a young man. The resemblance to eczema is limited to the nucleation of the horny cells, which compose the scales and crusts, and which is not usually present in Ichthyosis. But the crusts are much drier and firmer than in eczema, they contain much less fibrin, fewer leucocytes, and no morococci. The young horny layer surrounding the crust has once more the stamp of the ichthyotic basal horny layer, *i.e.*, there follows directly, on a single defective layer of granular cells, a particularly thick, homogeneous, completely a-nuclear basal horny layer, without transitional cells above or below. The prickle layer consists of well-preserved, deeply stained cells, showing, as far as the granular layer, no suggestion of intercellular cavities,

vesicles or spongy transformation, and very few leucocytes are found in it. On the other hand, the horny taps of the follicle mouths and sweat pores, seen in most sections, as well as the many horny pearls inside the epithelial ridges, indicate that we are not dealing with an eczema, but with a process distinctly tending to hyperkeratosis. Where the inflammatory process has not very deeply affected the epidermis, the crusts lie above these horny bodies and leave them intact; but when a deeper scaling of the epidermis has taken place, they fall off with the crusts, and leave behind a surface, beset with hollows, such as is not seen in eczema.

The changes in the cutis in serpentine Ichthyosis are less characteristic than in the milder, atrophic form. The cellular infiltration is more pronounced, not in the greater richness in cells, but in their greater protoplasmic contents. At limited spots along the vessels we meet collections of plasma cells, something like those in very old eczema. The number of mast cells is also somewhat increased. In the papillæ the number of cells is not greatly increased; this circumstance, as well as the absence of greater œdema, of lateral swelling, and of an increased amount of leucocytes, further distinguishes the papillary body of inflammatory Ichthyosis from that of eczema.

Of the other symptoms inside the cutis, the epithelium of the coil glands appears to be less functionless than in the milder Ichthyosis. One certainly finds here, narrow, adjacent, bladder-like loops, but the lumina are of normal width, and the epithelial cells are not all swollen and glassy towards the lumen, but chiefly normal. Mitosis, which is often present in the surface epithelium, I have not found in the coils. Otherwise the conditions are as in ordinary Ichthyosis.

It is thus clear that the eczematous stage of many cases of serpentine Ichthyosis is not identical with ordinary eczema, and especially not with the seborrhœic form, but that it represents an independent "ichthyotic catarrh." It is a matter of taste whether we should speak of ichthyotic eczema; the term has been introduced, and will probably be retained, clinically. One must consequently become accustomed to speak of different eczemas, as of so many moist catarrhs of different origin.

3. *Ichthyosis hystrix.*

True Ichthyosis hystrix is a very rare disease, and I state once more, that the nævi lineares (neuropathici) cornei, usually described under this name, have nothing to do with Ichthyosis, and observations made on them only lend support to errors in the anatomy of Ichthyosis. On the other hand, there is no doubt that there are true cases of Ichthyosis, in which horny and spiky protuberances develope on

different parts of the body, out of the flat lozenges of Ichthyosis. These are cases of serpentine form, and one may observe all the transitions from broader, flatter, into smaller and higher, horny-like outgrowths. Tommasoli has recently published a case of Kapos's, of this nature (Ueber autotoxische Keratodermiten. Dermatol. Studien, 15 Heft, 1893, L. Voss, p. 69); Ichthyosis serpentina of the knee and Ichthyosis verruco-hystricea of the arms, legs, and face. But I cannot admit as one, the well-known case of de Amicis, which Tommasoli quotes as parallel, even if the contact and flexure areas were free, for there were only erythematous spots around the horns, as in Neavus linearis, hydrosis was well preserved, steatosis increased, the eruptions did not develope on a generally ichthyotic skin, there was severe itching, and so on—it was a unique case of generalised keratoma. To this the histology of the case also corresponds; by the kindness of Prof. Tommasoli, I have sections, on which one can recognise that the type of cornification is quite different to that of Ichthyosis. The horny layer around the horn is not altered; the keratoma is not seated on ichthyotic skin. Inside the altered part there is a predominant hyperkeratosis, which is not simply limited to a firm connection of the horny cells, for there exists everywhere, not only a continuous granular layer, but inside the ridges the thickened horny layer shows a central layer of the ordinary loose structure, and only over the apices of the papillæ is it condensed into homogeneous layers. Where several papillæ are closely arranged together inside the keratoid plate, the corresponding group of smaller ridges forms the base of a steep walled cutaneous horn. In relation to the type of cornification, these hornlets are nearest to the ordinary cutaneous horns; there is found only an alteration in the quality of the horn, in relation to the papillæ, and between the papillæ, almost normal structure of the horny substance. Consequently, the individual epithelial cells are not atrophic, although the prickle layer, as a whole, is thinned by the deep penetration of cornification. The granular layer of the follicle neck is thickened, but the follicle is otherwise unchanged, and its epithelium is normal. The sweat pores inside the horny plate are not closed, but abnormally wide; the loops of the coil glands, on the other hand, are unchanged. The tissue of the cutis, as a whole, is normal, cellular infiltration does not exist, or in scarcely noticeable degree, in the papillary body. In short, everything typical of Ichthyosis is absent, and what is present everywhere points to a circumscribed generalised keratoma.

The more exact histology of Ichthyosis hystrix, in the stricter sense, is thus still to be described. The material available to me is not suitable, and I have consequently gone more thoroughly into the case of de Amicis, in order to simplify the differential diagnosis for

observers of suitable material, and so, on my side at least, not to do anything to increase the confusion, which has lasted all too long.

Otherwise it is not difficult to draw up a sketch of the appearances to be expected, for these cases clinically develope from serpentine Ichthyosis, and these latter now and again show a tendency to the formation of horns. If, at a circumscribed spot, the acanthosis ceases, while the hyperkeratosis, proper to Ichthyosis, persists (thus most easily in old people), then there must develope circumscribed, horn-like protuberances. And one will no doubt find diffuse changes of the horny layer, absence of the granular layer, cellular infiltration, and so on, in the surroundings.

We cannot leave the histology of Ichthyosis without reference to the efforts of Leloir to establish for this affection a place in the trophic skin affections. In two cases of serpentine Ichthyosis he found a degenerative neuritis of the peripheral cutaneous branches, with disappearance of the axial cylinder, breaking up of the medullary substance, and nuclear proliferation. In one individual the same degenerative change was also present in the spinal roots, more in the posterior than in the anterior. We cannot ascribe these otherwise unique observations to the account of the ichthyotic process, for similar ones have been described in quite other dermatoses, and specific nerve lesions are only available in the explanation of specific skin diseases, if the former give sufficient ground for the latter. But it can by no means be denied that, under the influence of nerve injuries, anomalies of cornification and circumscribed hyperkeratosis may develope, like other skin diseases, although the *direct* influence of the nerves on the changes in the skin must always remain open to discussion. But with Ichthyosis these rare conditions have nothing to do. At all events I have found the nerves normal. Campana, using Ehrlich's methyl-blue method, found the terminals of the nerves normal in the atrophic skin of ichthyotics. There is, therefore, little prospect that a definite histological basis for a nervous connection will be found in Ichthyosis.

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Porokeratosis.

This disease has been recently described by Mibelli. It commences with callous spots of different size and form, but always surrounded by an uninterrupted horny border, which, at its angle, has a linear horny ridge. An especially large spot on one of the patients covered nearly the whole forearm and back of the hand, in the form of a sharply margined, wavy streak. The extension is serpiginous, the centre usually sinks in somewhat, but remains callous, and is covered with scattered horny bodies. The seats of predilection are the backs of the hands and feet, then the rest of the extremities, the neck, face, and scalp.

The process commences with an acanthosis of the surface epithelium, to which soon succeeds a marked hyperkeratosis,* which, when the former diminishes, leads in many places to an atrophy of the prickle layer. In these places, the follicles and the sebaceous glands also atrophy, at least so far as the spots are found on skin with lanugo hairs. Then—and here is the distinction from hyperkeratosis—it affects mainly the sweat pores, which are filled by a black horny layer, first canalled, afterwards solid. This sinks deeply into the commencement of the dermal duct, and also reaches over the horny layer. By the coalescence of these poral horny bodies, developes the horny ridge, which distinguishes the advancing border of the affection. At the same time, there is, in the more recent parts, dilatation of the papillary vessels and cellular infiltration of the papillary body, extending outwards along the ducts of the coil glands, which show a dilatation of the lumen. Later, new collagenous tissue appears between the loops of the coils, and gradually leads to their atrophy. The rest of the cutaneous tissue also gradually atrophies, and thus the spot sinks in the centre. Mibelli compares this atrophy of the coil to cirrhosis of the liver, from ligature of the bile duct. He ascribes the dilatation of the duct to the terminal plugging of the sweat pore, and regards the atrophy of the coil as the ultimate symptom of this retention process. Here it must be noted that other affections, where the sweat pores are plugged, do not show cystic dilatations of the duct, and still less does an atrophy of the coil always follow. For this reason, and also in view of the cellular infiltration described by Mibelli on the surface and

* In his description Mibelli incorrectly identifies the basal streak of the horny layer, which is not blackened by osmium, with the whole of Oehl's stratum lucidum, and calls the under black streak of the black border (Ranvier), super-basal layer, while it really represents most of the basal layer. Although not long ago (Zwei vergessene Arbeiten, etc. Derm. Studien, 1889) I called attention to this common error, I must mention it once more, for the, otherwise very accurate, work of Mibelli might further aid the confusion. Oehl's "stratum lucidum," my "basal horny layer," comprises normally three or four rows of cells, of which, when treated with osmium, only the lower remain unblackened. "Super-basal horny layer" I have named the rows directly above the basal ones (in thick horny layer), for they do not show quite the same colour reaction as the rest of the middle horny layer.

around the coil glands, I must regard the whole affection as a chronic inflammatory one. It is, I believe, closely related to the group of lichen—pityriasis rubra pilaris—ichthyosis, and corresponds, in the peripheral extension of its fine abrupt border, most closely to Lichen annularis.

Respighi (Pisa) has observed eight cases of this affection, which is apparently not uncommon in North Italy. He distinguishes, miliary to lentil sized papules, nummular patches (especially on the legs), and circinate patches. The latter are most frequent, and in many cases are present alone; their border is regular, polycyclical or zig-zag, they are sometimes composed of miliary projections. Cones, three to four millimeters high, are only found on the tips of the toes. There is never an inflammatory halo, but the centre of the circinate patches is sometimes reddened. The nails are secondarily affected, are cloudy, thickened, brittle, and may completely fall off. The affection has a dry character, and does not readily react to medicaments. Respighi found spots on the palms and soles.

Respighi describes the hyperkeratosis like Mibelli, but lays more stress on the horny taps which penetrate the follicles, and reach close down to the acini. In the ducts of the coil glands, underneath the poral horny cysts, he finds no dilatation, but a narrowing and here and there ampullated dilatations on the coils. In the miliary papules, and on the border of the circinate patches, he invariably found a central depression, or a furrow, which corresponded microscopically to a follicular or tubular horny tap, or to the space between two such taps. The marginal wall consisted either simply of thickened horny layer, or the thickened papillæ also shared in the formation. The atrophy of the prickle layer and granular layer with thickening of the horny layer in the centre of the circinate papules, the slight cellular infiltration in the centre, greater at the border, the atrophy of the coils, hair follicles, and the cutis, Respighi describes like Mibelli; but according to him the sebaceous glands may even hypertrophy. He thinks we have probably to do with a parasitic hyper- or parakeratosis of the mouths of the tubular and acinous glands. He compares the affection, in its serpiginous advance and its preference for the backs of the hands and fingers and the nail fold, to the ordinary wart.

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Acro keratosis (*Acrokeratoma*, Neuburger).

Under this name I present a case of Neuburger's, which showed a *hyperkeratosis*, especially of the extensor sides of the extremities, and *most marked on the*

backs of the hands and feet. Neuburger named his case *Acrokeratoma hereditarium*,* since he believed that it was histologically less related to Ichthyosis than to the keratomata ; after thoroughly considering his observations, I must draw the opposite conclusion, and place the case very near Ichthyosis. This different conclusion depends mostly on the fact that Neuburger made his comparison with Ichthyosis from the observations of various authors, all of which by no means related to Ichthyosis.

The skin of the whole body was yellowish-brown, rough and dry, never perspiring, except on great heat, and only in the axillæ. On the extensor surfaces, especially on the backs of the hands and feet, it resembled chagreen leather. The hairs were short and bristly. The skin on the back of the hands was in winter, black, in summer, not so dark : the hands and feet were always cold. On the backs of the hands, and still more on the backs of the feet, the skin could only with difficulty be moved and pinched up, thus giving the impression of a sclerodermia. The passage of the rough regions into the healthy was very gradual. In this, as well as in the symmetry, the heredity, the dryness and the very diminished sensitiveness to pain, temperature and electricity, the case, apart from the peculiar localisation of the hyperkeratosis, recalled Ichthyosis. It appeared in three generations.

Neuburger found the epidermis thickened to six or eight times the normal, the prickle layer only very moderately, the horny layer excessively ; it appeared at the same time yellowish brown, at the outermost edge dark brown. The sweat pores formed in it thirteen to sixteen turns and were much dilated. The super-papillary prickle layer was thinned, down to two or three rows of cells. Only the basal prickle layer was well marked and contained mitoses. The granular layer was much thickened, varying from three rows over the papillæ to eight in the depressions between them. The elëidin was somewhat increased, but not in anything like the same degree, as the keratohyalin ; it extended along the sweat pores to the last layer.

The main distinction from Ichthyosis is in the special development of the granular layer, for Ichthyosis nitida shows no granular cells, Ichthyosis serpentina no great increase of them. In the main, this Acrokeratosis can only be compared with the later forms of Ichthyosis, both from the clinical appearance (crocodile skin, no spontaneous scaling) and from the histological (abundant mitosis, thickened prickle layer). Consequently there is present an unusual process of cornification.

Neither in the cutis nor in the papillæ did Neuburger find, apart from a slight perivascular cellular infiltration, any appearance of growth. The elastic tissue is thin, and in the depths of the skin remarkably fine ; the collagenous tissue is firm, and poor in vessels. This description holds, without change, for many cases of Ichthyosis. Neuburger, however, expected in Ichthyosis collections of pigment, " twistings of

* Mon., Vol. XIII., p. 1, 1891.

the vessels," and, according to Neumann, hypertrophy of the whole cutis, which were not present in his case. But in truth these statements refer partly to "local Ichthyosis," partly to Nævi cornei, and are by no means characteristic of Ichthyosis. Why the author does not admit the slight, perivascular, cellular infiltration as a sign of slight inflammation, as we do in Ichthyosis, is not very clear. The appearances in the cutis very closely resemble those of slight Ichthyosis. Neuburger found around the coil glands a well-marked interstitial chronic inflammation, in the form of cellular infiltration, and, in relation to it, the epithelium of the coil glands in parts degenerated.

In contrast to Ichthyosis, Acrokeratosis leaves the hair follicles alone ; it never leads to hair cysts. The panniculus is very atrophic, thus further corresponding with the condition in long-standing Ichthyosis. Finally, Neuburger found, at a circumscribed spot of the excised portion, the prickle cells increased to five times their normal size, their prickles gone, the cells coarsely granular, with obscure nuclei, and, here and there in the upper layer, a few hyalin degenerated, a-nuclear epithelial cells. These latter symptoms, as well as the cellular infiltration, especially that around the coils, and the rarefaction of the elastic tissue, can only be united in the assumption of a slight inflammatory infection, and I cannot regard the placing of Acrokeratosis among the keratomata, especially beside Keratoma palmare hereditarium, as justified. Neuburger recognised the clinical differences from the latter, and supports his views chiefly by the histological examination. But this only shows a relation to Ichthyosis. From that, Acrokeratosis is chiefly distinguished by the thickness of the granular layer, the normal behaviour of the follicle, and the scattered degeneration of the epithelium.

Parakeratosis variegata.

A rare, very chronic disease, which I have twice noted. Breast, neck, abdomen, back and finally extremities are affected by yellowish to brownish red spots and flat papules, always increasing in number, which are partly sharply marked off from the surroundings and roundish, or are connected by processes, by which a net-form or marbled, variegated appearance of the affected region of skin is produced. The scarcely elevated papules are either covered by a thickened, smooth, horny layer, and are then like lichen, or they carry fissured scales. There is scarcely any infiltration of the cutis. Subjective symptoms are absent ; the affection is strikingly resistant to local treatment.

Santi and Pollitzer each examined in my laboratory one case of this nature ; their observations agree in the main. The affection is limited to the epidermis and the papillary body. The cutis proper, the follicles and coils, muscles and hypoderm are normal. The papillary body shows moderate dilatation of the vessels, and œdema, but only a

slight chronic inflammation, characterised by multiplication of the perithelium, while proportionately few leucocytes escape. The prickle layer is slightly thickened, not by new formation of epithelium, but by intra-epithelial and still more by inter-epithelial œdema. The lymph spaces are transformed into wide canals, frequently with diminution of the adjacent epithelium; sometimes the nuclei in that are œdematous. This inter-spinal œdema ceases in the upper part of the prickle layer. The granular layer is well developed; the thickened horny layer runs flat over the wavy papillary body, without following its depressions. This tension of the horny layer above the œdematous prickle layer and the œdematous papillary body explains the lichenous burnish of many papules. The dilatation of the lymph canals of the epidermis extends directly into the analogous change of the papillary body. The œdema extends in its full development to the horizontal distribution of the papillary circulation, and from here outwards diminishes along the dilated vessels, which penetrate the cutis, but disappears, though not completely, in the lymph spaces of the cutis itself.

We have consequently to do with a superficial inflammation of the skin, which is accompanied by unusually severe œdema of the papillary body and the epidermis. The latter is shown by a thickening of the horny layer and a slight formation of scales.

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Hyperkeratosis subungualis.

This affection, described by H. v. Hebra, possesses a special scientific interest, for it is strictly limited to the nail bed, and affects the nail plate, either not at all or only very late and to a slight degree. It therefore shows, better than the ordinary diseases of the nail bed (eczema, psoriasis), which usually early attack the nail plate, that the nail plate, in regard to its nourishment and proliferation, is quite independent of the nail bed. In the course of a few months all the nails of the fingers and toes were attacked and elevated from the nail beds, from the anterior end of the lateral fold onwards, by a thick, brownish or greenish black, loose, horny mass. This abnormal, $\frac{1}{4}$ to $\frac{1}{2}$ centimetre high, horny layer gradually extended over the whole nail bed down to the lunula, though usually only on certain fingers. Then the nail plate is also here and there cloudy, and split into lamellæ; but usually it retains its burnish, its normal thickness and transparency, and is only made wavy by the different thickness of the horny layer at different places. Usually the horny layer of the end of the finger is also affected, split and scaly. The points of the fingers usually show paræsthesia. The affection is very chronic and obstinate.

My material comes from a typical case, in which I removed by operation all the finger nails, along with the horny layer of the nail

bed. On looking at the nail from the under side, the nail plate is seen to be everywhere sound, firm, transparent, of normal thickness, and only very much bent. The pathological horny mass is firmly adherent to it, but is everywhere sharply margined from it, is cloudy, brittle, soft, and fissured. One can always recognise on it, especially with the aid of a lens, a longitudinal striated appearance, following the normal longitudinal ridges of the nail bed; and transverse section of the nail shows the arrangement of the subungual horny layer still more plainly, by a well-marked undulating appearance. The horny mass is always thickest (up to $\frac{1}{2}$ centimetre) at the anterior borders, especially at the lateral angles; it diminishes posteriorly and towards the middle, and gradually disappears in the region of the lunula.

Longitudinal, transverse, and horizontal sections show that in some nails the process has occurred inside the cutis of the nail bed. One sees in cross sections, papillary-like, vascular processes extending into the horny layer, which, in horizontal sections, may be recognised as sections of much increased ridges. They are only a little broader than the normal ridges, but are very much higher. They are closely packed with spindle cells and leucocytes, which wander into the epithelium from the upper angles of the ridges. The sub-epithelial plate of the papillary body, which is here and there preserved, is thickly infiltrated with cells. The prickle layer of the nail bed is thicker than normal, both the part between, and that over the ridges. It passes, above, into the horny layer without any sharp margin; there is great flattening of the cells, but no suggestion of granular cells. The horny cells consequently retain their nuclei, even the oldest ones, which are adjacent to the nail plate, into whose undermost layer they appear to be pushed. In general, they increase in size towards the surface, and sometimes acquire gigantic dimensions, their substance swelling under the influence of an exudative process, without breaking down. They are concentrically arranged around the ridges of the cutis of the nail bed, and are arranged in very many (twenty, fifty, even to a hundred) layers, with a slight tendency forwards. Their regular undulating form is—as in cutaneous horns and all gryphotic processes—interrupted by two circumstances; on the one hand, by the enclosure of nuclear masses, which are certainly mainly supplied by leucocytes immigrated into the epithelium, and appear in layers between the horny lamellæ, in a very irregular manner, and on the other hand, there is formed over the ridges, exactly as over the papillæ of the cutaneous horn, a sort of spongy medullary substance in the horny masses lying above. This medullary formation results from the swelling and dissolution of groups of adjacent horny cells. But in most of the medullary columns, lying deep under the

nail, there is no secondary drying with penetration of air, and therefore they have a somewhat unusual appearance. There are nests of light, bladder-like, spherical, epithelial cells, which are sharply marked off from the other lamellar, cloudy, flat layers of cells.

But there is still a third factor which interrupts the regular piling up of the horny layer of the nail bed, the immigration of swarms of cocci. These are only found in the uppermost horny layers, and completely fill flat, irregularly formed, inter-communicating spaces, whose extension is demonstrated by sections in different directions. Horizontal sections of the uppermost horny layers show that their extension corresponds to the spreading of the hyperkeratotic process, underneath the surface of the nail plate; longitudinal sections, that they are limited to the upper third of the horny layer, sink somewhat deeper towards the posterior end of the diseased epidermis, while at the anterior nail border they are found, quite superficially, under the nail plate; transverse sections show this position, and also their immigration from the under surface of the nail plate, in the lateral folds, towards the middle of the nail.

The cocci are pretty large, ·8 to 1·2 μ, arranged in clusters, and sometimes also in chains of three or four cocci in the narrower horny fissures. From the staphylococcus aureus they are chiefly distinguished by their regular *spherical form*, and the *absence of leucocytes in their immediate neighbourhood.* They appear to effect a softening influence on the horny cells, for though there is no formation of vesicles, with increased liquid exudation into the horny spaces, the horny cells surrounding the masses of cocci are cloudy, badly stained, and swollen.

It is, in short, an organism which is as different from the ordinary eczema coccus, as from the ordinary pyococci. Since, further, its extension corresponds exactly to that of the subungual diseased process, and its peculiar nature fully explains its commencement from the outer border and its extension under the nail plate, it is very probable that we have to recognise in it the cause of Hyperkeratosis subungualis. In this case we have to assume that specific cocci, which find in the loose horny cells of the anterior and lateral nail folds, but not in the nail cells themselves, a suitable medium, are here deposited, that they induce the inflammatory exudation in relation to the nail border and the anterior part of the end of the finger, and then advance under the under-surface of the nail plate, leaving everywhere a dry cutaneous catarrh, with acanthosis, and a horny layer of parakeratotic type. The process may be compared to those diseases of the hair, in which the prickle layer of the hair follicle, but not the hair shaft, is diseased and which tend to over-production of horny substance.

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Onychoses Parasitariæ.

The chapter of the cutaneous catarrhs of the nail, although not neglected since Virchow's work on Onychogryphosis and Onychomycosis (1854), is still, on account of the want of material for examination, one of the emptiest in the histology of the skin. This is much to be regretted, for the constant supply of pathological horny substance, supplied by the nail, might evidently permit of many conclusions as to the less easily explained, finer conditions of the superficial horny layer, in corresponding diseases of the general surface. But certainly we are in a position, with the normal anatomical conditions before us, somewhat to arrange, from the macroscopic relations, the finer facts, and where the positive microscopical observations are still awanting, I shall have in the following survey to follow this plan, in the expectation of future control by microscopical examination, and with the wish to present the clinical material to the pathologists in some sort of order. I regard, as of chief importance, the adoption of a strict division between the pseudo-onychogryphoses, as accompaniments of the infectious catarrhs, whose parasites will probably be readily recognised in the nail, and the true onychogryphoses from trophic disturbances and deformities of the nail. The latter are found under hypertrophies of the nails.

Favus of the nails is as yet the best known parasitic onychia. It shows the same two periods, with differences of growth, as favus of the epidermis, that of surface catarrh and that of the scutulum, in other words—that of limited and unlimited development of the fungus (see Favus). But there exists the very important difference, that in the nail, the superficial catarrh of the nail bed, protected by the nail plate and evidently under much better conditions of nutrition (greater warmth and moisture), is the common form, and, in contrast to Favus of the skin, an eminently chronic disease. In many cases it lasts years longer than Favus of the head. Evidently the fungus finds, in the horny layer of the nail bed, protected by the nail, a still better hiding-place than in the hair follicle, and here it enjoys, without scutular encapsulation, undistributed growth. Since the scutula arranged over the nail bed can only have arisen on the basis of a previous superficial existence of the fungus, one is still justified, even in favus of the nail, in speaking of a period of superficial catarrh, and of a scutular period, although both are excessively chronic in their course.

Forty years ago Virchow clearly described, from the corpse, the two forms; the first as leafy, subungual horny masses, beset with fungi, of a yellowish

white, cloudy, transparent appearance ; the second, further back, as quite dry, dirty whitish, yellow, powdery, scaly, rough, dead-looking areas, close in front of the lunula ; in one case, on pulling back the nail plate, there was a fine dust. In life, one finds in the former cases, the nail plate elevated, from the anterior border of the lateral folds, by a dirty brownish or greenish horny mass, more movable than normal, arched but otherwise healthy, transparent and smooth ; in the other cases there shine through the only slightly elevated and cloudy, but not so much discoloured nail plate, sharply circumscribed, yellow, isolated areas. Fabry once found the first form on a finger, the second on a toe nail.

In two cases of favus of the nails I found the horizontal extension of the favus mycelium in the first horny layer of the nail bed, which had developed under the influence of the fungus growth. The prickle layer of the nail bed is thickened, its hypertrophic ridges pass, in front, before the border of the finger pulp is reached, into a very steep-walled ridge system, with long drawn-out papillæ and an enormously thick horny layer. At this anterior margin the fungus threads are more sparing, and first increase further back and inwards. Under their influence the heaped-up horny layer of the nail bed is split into lamellæ, which show different degrees of cornification, and sometimes a perfectly normal, superficial cornification, by means of a granular layer. Here, as on the skin, the favus fungi do not go boldly into the epithelium, but only into the cornified epithelium, and extend only their terminal processes, like feelers, into the uppermost cells of the uncornified prickle layer of the nail bed. This circumstance has been overlooked by some authors, because the subungual horny layer partly shows different staining reactions to the horny layer of the surface, and because the thickness of the horny layer, in many places in the nail bed, is much greater than that of the prickle layer. Inside this horny layer the fungi are arranged in an exquisitely reticular form, *i.e.*, they grow through the horny layer, parallel to its layers with their long processes, and at right angles with their cross bridges. There is never found a formation of oidioform spores, but one certainly sees dying mycelium and involution forms in the upper and anterior, *i.e.*, the older horny lamellæ.

In one of my cases the nail plate, running over this horny layer, is completely intact, as it is usually said to be by other authors. Bearing in mind that favus prefers anærobic growth and warmth, this immunity of the nail plate is not remarkable ; its greater hardness will no more prevent it from being permeated by the fungus, than the cuticle of the hair and the hair shaft are protected by their hardness. Of course the nail plate, though loosened from its base, does not usually fall off, but remains adherent at the root.

But the disease of the nail plate does not usually appear to come,

even *indirectly*, from the nail matrix, for all authors admit, that the diffuse growth, as well as the formation of scutula, stops at the border of the lunula. But a case of extensive disease of the nail, for which I thank Dr Eddowes, shows that the nail matrix may be affected by Favus in its whole extent. Here also the hyphæ only grow in the horny layer of the matrix, down to the lowest end of the posterior fold. It is quite apparent, that in such circumstances the retention of the nail plate is impossible, and in this case—whether with or without previous attack by the fungus, is impossible to decide—it is gone. The nail bed was covered only by a thick horny layer, full of fungi, and split into lamellæ. In some parts of this nail bed I found a denser collection of mycelium, which I would regard as the commencement of scutulum formation. Here the prickle layer is thinned down to small, trough-shaped grooves, being compressed by the mycelium on all sides. The threads cross each other, but so closely, that very few horny cells are present in their meshes, and the lowest mycelium is arranged, with perpendicular processes, on the trough-shaped depressions of the prickle layer. These two appearances suggest scutulum formation (see Favus). But this collection of fungus is far from being a true scutulum. There is absent, first, the parallel, right-angled direction of all the mycelium and the separation of spores in a central space, and finally the complete exclusion of the epithelium. But one at least recognises, that the latter is so far developed, that the formation of new horny cells does not keep pace with the growth of the mycelium.

Future investigation must better determine, histologically, the nature of the subungual scutulum. There do not appear to have been any sections made through them.

The subungual cutis shares in the process, in my case, with a marked growth of cells and dilatation of the blood vessels. In the second very extreme case, the lymph spaces of the cutis are extraordinarily wide, as in favus of the scalp. The long persistence of actual scutula under the nail plate will, of course, lead to atrophy of the skin after healing.

Trichophytosis of the nail begins, like Favus, regularly at the anterior border or the lateral fold, and leads to elevation of the nail plate. In contrast to Favus the latter does not take the dark brownish, blackish colour, but remains whitish-yellow, and further—although only after a long time—is finally always affected; it becomes opaque, rough, is irregularly lined, split, and finally falls off. It is very much rarer than Favus of the nails, and possibly requires other preceding skin catarrhs to prepare the soil (Eczema, Psoriasis of the nails, according to Besnier-Doyon).

C. Pellizari found the extension of the fungus analogous to the

superficial extension of Favus. But he determined also its presence in the nail plate in small areas, which corresponded to macroscopically visible, opaque spots. The investigation of Trichophytosis of the nail must be undertaken again with the newer staining methods.

Eczema of the nails is usually a combination of disease of the nail bed and the nail matrix, and the appearances developed are very different. Simplest, and most easy to explain, are those cases in which the nail plate is elevated, at the anterior free border and in the lateral folds, by a loose, mostly dark-coloured horny mass. It there remains, at first pretty normal, but gradually becomes looser, thicker, cloudy, and dark. These cases approach Hyperkeratosis subungualis, but differ from it in the secondary changes of the nail plate. They correspond, beyond doubt, to a primary, eczematous affection of the nail bed which extends from the distal end towards the proximal, without reaching the latter. This form I have especially met in universal, dry, long-standing, seborrhœic eczemas.

The greatest contrast to this is supplied by those cases, in which, in severe inflammatory, moist, or œdematous eczemas of the finger, the posterior and lateral nail folds are first attacked, and from them the nail. Perionychia may be recognised by redness, swelling, and tenderness of the nail fold, from which a sero-purulent fluid can sometimes be pressed. The whole nail plate is loosened from the region of the lunula outwards, and is more movable than normal; it swells up, becomes white, opaque, yellowish or brownish, and scales on the surface, leading to the formation of small, circular or longitudinally-grooved exfoliations. In long duration of the disease, the exfoliation, overcoming the growth, may very much thin the nail plate, especially in its anterior part. This pretty pure form of eczematous disease of the matrix, identified by the changes being almost limited to the nail plate, is relatively rare.

More frequent is the mixed form, in which the perionychitic symptoms are in abeyance, the disease of the matrix milder and more stealthy, but, on the other hand, symptoms of the disease of the nail bed are early seen. Then one notes, at first on the lunula, whitish areas, over which the nail substance is softened and distended. By extension they run together into long elevations. By exfoliation of these softened areas, there develope, as the nail plate advances, sometimes circular grooves, sometimes linear depressions. The nail plate on the surface becomes rough and dull, without showing the same great thickening and discolouration as in the previous form. But there sets in, from the anterior and lateral borders, an undermining of the nail plate by a loose, dry, horny mass, which elevates it here and there,

but does not lead to separation of the whole plate from the nail bed. By these subungual parakeratoses, the nail becomes as a whole distorted and thick, especially at its anterior border. After the disappearance of the eczema it becomes drier, and thus, and by exfoliation, diminishes in volume, acquires a brownish, black, once more transparent appearance and a coarse-pored, worm-eaten surface, and tends to separate itself in a sharp line from the new-formed, healthy, transparent, shiny nail substance. All forms of eczema of the nail, but especially the last two, are combined, if they last long, with changes of the subungual cutis. According to the point of attack of the eczema, certain segments, underlying the nail, are affected by inflammatory œdematous swelling. The region of the lunula in particular, and then that of the anterior border, form cushion-like swellings, over which, slightly bent, the diseased, altered nail runs. On these depend the transverse depressions of many eczematous nails, which—in contrast to the transverse lines of typical psoriasis of the nails—have nothing to do with changes of the nail cells.

The main symptom of Eczema of the nail is the punctiform or diffuse softening of the nail substance, a symptom completely comparable to the parakeratosis of the surface epithelium in Eczema. The isolated observations on sections of nail, by Spillmann (quoted by Ancel) would correspond with this view; unfortunately they were limited to the subungual horny layer, and did not extend to the nail plate, which in that case was normal. Spillmann found a net-like arrangement of the horny substance, cavities arising from the degeneration of the nail cells being filled with serous fluid, and enclosed by horny septa.

This softening of the horny substance extends, in Eczema, more readily than in other cutaneous catarrhs, directly to the formed nail plate. It leads to clouding and thickening of the nail. Two further processes, the cushion-like thickening of the subungual cutis and the advance of the subungual horny layer, which, as is easily seen, have their analogies in Eczema of the surface, tend to partial thickening of the nails. On the other hand there constantly underlies the softened nail, an abnormally great and irregularly arranged scaling, which prevents the accumulation of nail substance. From these symptoms are combined the varied pictures of eczematous nails, whose sign manual is their irregularity.

Psoriasis of the nail is, as is easily understood, very closely related to Eczema of the nails, and is only distinguished by its dryness and its regular formation. Here also one has first, the very frequent, isolated Psoriasis of the nail bed, which extends from the free border of the lateral nail folds under the nail plate, and elevates it by a dry mass of

scales. Since the nail plate in Psoriasis remains drier and harder, the elevation has a greater effect than in Eczema; the Psoriasis papule under the nail "levers" the whole nail plate "up," and thus air gets under it, a large extent of the nail plate becoming opaque, yellow, and later, darkly coloured. To the cloudy, loosened "white spots" of Eczema there correspond, in Psoriasis of the nail plate, areas of softening, which are however smaller, and on exfoliation leave a smooth, rounded depression on the surface, to which a dried-up, mortar-like fragment of softened horny substance frequently adheres. But there fails, almost or entirely, the diffuse softening and thickening of the surrounding parts of the nail plate, and therefore the coarse furrowing in the form of long ridges and furrows. The nail plate, as a whole, retains its hardness, transparency, and smoothness. The above-mentioned smooth grooves thus appear all the more definitely, and there is a certain justice in regarding these, when they are numerous, as Psoriasis of the nails ("κατ' ἐξοχήν"). They appear in relation to the lunula, sometimes in semi-lunar rows, and arrange themselves as the nail advances, in regular longitudinal series, from which it is seen that they correspond to definite points of the nail matrix. Most probably they form, like the "white spots" in the nail plate, in Eczema of the nail matrix, above individual papillæ. In favour of this is the observation, recently made by Schütz, that in many cases, visible red points in the nail matrix, *i.e.*, dilated capillaries, correspond to them. Sometimes without these grooves, sometimes in addition to them, there exists a wide-spread, linear softening, which, like Psoriasis, appears intermittently in relation to the lunula, and thus gives origin to perfectly regular, transverse furrows on the surface of the nail. These also are, to a certain extent, characteristic of Psoriasis of the nails, in contrast to Eczema, since the large transverse swellings, with bending of the whole nail plate, which are induced in Eczema by the swelling of subungual tissue, are absent in Psoriasis.

The distinctions between Psoriasis and Eczema of the nails consequently depend on this, that in the former the nail softening is limited to punctiform and linear segments, and the nail plate, as a whole, remains drier and harder, that the diseased areas thus show a regular distribution over the surface of the nail, and that, in the subungual cutis, great dilatation of the blood vessels appears, instead of inflammatory œdema (in Eczema). They are exactly the same distinctions, which we find, in general, between Psoriasis and Eczema, and I can only say here, as there, that Psoriasis of the nails simply presents an extreme border type, which is combined by innumerable slight transitions, with the different types of Eczema, so that the apparent differ-

ences are not so much related to the nature of the diseased processes, as to the difference of the soil in individual cases.

Pityriasis rubra pilaris of the nails resembles psoriatic Onychia. Here also there are grooves and linear transverse exfoliations, but at the same time the nail plate, as a whole, becomes cloudy, shows distinct longitudinal furrowing, and is often elevated from the anterior border by a considerable subungual horny wall as far as the middle of the nail. The nail plate grows quickly, and meets, in the piled up subungual horny mass, a resistance to which is probably due the peculiar tenderness in Pityriasis rubra pilaris. There is never an exfoliative thinning of the nails, as is frequent in Psoriasis, and still more so in Eczema of the nails.

The other dry skin catarrhs resemble these affections in their influence on the nails, especially the varieties of Lichen, Pityriasis rubra, Dermatitis exfoliativa, and Parakeratosis scutularis. Until histological investigations are made, one must deduce the different appearances from analogy.

Darier's psorospermosis deserves special notice among these affections. Boeck has recently noted the invariable affection of the nails. The nails are thickened, opaque, longitudinally streaked, fragile at the anterior border, and usually bent upwards.

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(bb). *Deep Inflammations of the Epidermis.*

Deep inflammations of the epidermis comprise (*conf.* p. 157) those inflammatory skin diseases, in which the infectious agent has its seat in the epithelial appendages; the follicles or coils. The former are much more easily and frequently affected than the latter; indeed, while the immigration of bacteria and fungi from the surface into the

entrance of the hair follicle has been proved to demonstration, clinically, experimentally, and histologically, one cannot yet regard Spiradenitis, from external infection, as a definitely established fact. The immigration into the hair follicles presents no anatomical difficulties, for both the horny substance of the hair itself, as it descends, and the fissure between hair and hair follicle epithelium, is open to microscopical observation; the only difficulty is in relation to the biology of each micro-organism. For these find in the depths of the follicle more moisture and warmth, and certainly less oxygen, and therefore all those bacteria and hyphomycetes, which are not very aërobic, and require a higher temperature, prefer to seek out the hidden depths of the follicle, and retain their position there, if they are removed from the surface of the skin by unfavourable external conditions. And so, as we have long known clinically, and can to-day prove at any moment histologically, the hair follicle is a perfect incubator for infectious germs, making their removal more difficult, and thus we regard, for example, Trichophytosis, as a slight affection, so long as it is limited to the surface epithelium, and does not reach the depths of the follicles.

With our extending knowledge of micro-organisms the number of folliculitides will probably increase. Already we are more or less familiar, histologically, in addition to the ordinary staphylogenic folliculitis (Folliculitis staphylogenes, Sycosis staphylogenes), with Folliculitis scrophulosorum, and etiologically with Folliculitis bacillogenes.* Possibly the Folliculitis exulcerans of Lukasiewicz should be placed here. Only a short time ago I had the opportunity of observing a quite unique, hitherto undescribed folliculitis of the female genitals. Much material, which has never been worked up, lies collected, especially in French literature, and a rich harvest here awaits experimental, bacteriological, and histological investigation.

It is quite otherwise with Spiradenitis, the primary inflammation of the coil glands due to infection from the surface. Here the anatomical nature of the entrance, and the relatively long, narrow canal, which, in contrast to the hair follicle, is constantly washed by a centrifugal stream, and therefore presents the greatest resistance to a centripetal entrance of organisms, opposes not a few difficulties. For we see, that these very organisms, which are exceptionally well adapted to the acid reaction and other peculiarities of the sweat, the flora of the flexures and the genitals, show no tendency to wander into the sweat pores, against the sweat stream. Where such an entrance takes place, there must come into play very powerful (chemotactic) forces, of whose method of action we are as yet ignorant. I certainly am not prepared

* Folliculitis bacillogenes Tommasoli, caused by the Bacillus pyogenes fœtidus, is not here referred to, on account of the absence of histological details.

to deny the possibility of an infectious inflammation of the coil glands, only in importance, it is a long way behind infectious folliculitis.*

Attention is only now being clinically directed in Germany to the presence of primary Spiradenitis, while a tendency has long existed in France to attribute localised, apparently cryptogenic, inflammatory, deep-lying nodules to inflammation of the coil glands, since Verneuil thus explained certain inflammations of the axillary cavity. Whether there really is such a Spiradenitis is not so easily determined as might appear, and depends entirely on histological examination, for the external localisation is not definitely indicated—as in folliculitis—by the hair in the centre. That the coil glands are affected secondarily in inflammations of the cutis (lupus), or of the hair follicles (furunculosis), is a very frequent and long familiar fact; but we are not dealing with that. But histological examination has, in reference to this fact, specially to exclude the possibility, that the coil glands in given cases are affected secondarily, *e.g.*, from the penetration of the infectious agent into the hair follicle; and it is further most important to study the first stages of the process, and to examine the sections serially. The commencement of the inflammation in a hair follicle does not definitely exclude the diagnosis of a true Spiradenitis, if only the inflammation has the power of affecting preferentially or solely the coil glands, and of continuing its extension chiefly to these. This circumstance would, nevertheless, bring with it, clinically as well as histologically, certain peculiarities, which would completely justify the maintenance of the definition Spiradenitis. And the recent attempts of Pollitzer, Dubreuilh, and others, seem to have succeeded in establishing such a well-characterised disease. I will therefore place them, in contrast to the group of folliculitides, as the single definite example of Spiradenitis, with the reservations made above.

That a Steatadenitis (inflammation of the sebaceous glands), as a separate affection from the different forms of folliculitis, does not exist, it is scarcely necessary to say. The same methods of entrance and the same infectious agents exist for the hair follicles and their glandular appendages, and altbough the well-known difference between the follicles with strong hairs and small glands, and those with large glands and small lanugo hairs, may lead to very definite microscopical distinctions, their separation into different affections (Folliculitis and Steatadenitis), with the same etiology, would be artificial and impossible. It is much easier to distinguish diseases of the same etiology, according as

* In the spiradenitides, in contrast to folliculitis, one must always bear in mind that the coil glands may be affected from within, by a separation of organisms from the blood. As yet this has not been determined. Separation of virulent pyococci by the sweat, although frequently assumed, is as yet by no means certain.

they affect the large follicles with strong hairs, or the small ones with lanugo hairs; in the staphylogenic infection such a distinction is requisite, both from clinical and histological aspects (Sycosis and Folliculitis staphylogenes).

The establishment of an infectious Steatadenitis would only be justified where the infectious agent entered the sebaceous gland alone, avoiding the (large or small) hair follicle. Such inflammations are as yet unknown. Diseases affect equally hair follicle and sebaceous gland.

Leaving aside this, as yet unripe, question of Spiradenitis, we have in the deep inflammations of the epidermis chiefly to do with folliculitis. New diseases of this sort should therefore all be described as folliculitis, with the addition of an appropriate adjective. But the question is of importance, how certain well-characterised affections of this nature, which have long been known under other names, are related to the other folliculitides.

As to Sycosis, it has already been suggested that we may very well retain this name for a special form of inflammation of the follicles with strong hairs, without losing the advantage of specially indicating the corresponding disease of the lanugo hairs, as Folliculitis staphylogenes.

In Trichophytosis the disease of the hair follicles is so dominant, that the description of a special Folliculitis trichophytica appears unnecessary. In view of the slight significance of Trichophytosis of the surface epithelium, I have described the Trichophytoses all together under the corresponding follicular disease. This was also necessary in Favus, although there the superficial disease shows much more characteristic and definite phenomena than in Trichophytosis. Nevertheless, I gladly admit that the arrangement of Favus, as a whole, under the deep epidermic diseases, depends as much on the recognition of the invariable deep affection of the cutis, as on the accompanying disease of the hair follicles.

Acne occupies a unique position. In the French school, still more than in the Vienna school, the definition of acne has gradually extended from the original, well-circumscribed disease to all possible varieties of primary and secondary folliculitides; indeed, to extra-follicular abscesses and to the most different varieties of functional disturbances in the separation of sebum. It has therefore become almost synonymous with folliculitis and affections of the sebaceous glands; that is, it means nothing definite. But we are not so rich in original names, that we should not retain the definition of acne as well as that of folliculitis, which latter gives more precisely the definition of inflammation of the follicle, and leaves room for new discoveries in this region. I have, therefore, long gone back to the narrower definition of acne, which

preserves its original character as representing a unique variety of folliculitis.

All other diseases, so far as they are inflammations of the follicle, I indicate with the name folliculitis and a suitable adjective, which permits of ready comprehension.

(a). *Inflammations of the Follicle.*

Acne.

Acne is an affection of the skin, limited to the cheeks, nose, forehead, chin, and shoulders, and to the period of puberty. It extends rarely to the whole back, still more rarely to other parts of the body (scalp, extremities); and usually disappears with adolescence. It is characterised in the first stage by a superficial hyperkeratosis of the epidermis, which, extending to the follicle mouths, leads to the formation of comedones. While the sebaceous glands with the follicles are stopped by horny plugs, the coil glands are active; indeed there is often Hyperidrosis oleosa. The skin is stretched by the unyielding horny layer, anæmic, little movable, and on the face not easily pinched up. Pressure causes, more easily than normal, a circumscribed spastic œdema. On this basis, (Acne punctata) a more inflammatory development of the disease takes place in two directions, one progressive, dry, and inflammatory, with thickening of the whole skin, hypertrophy of the sebaceous glands and the formation of inflammatory nodes (Acne indurata), the other accompanied by secondary suppuration of the sebaceous glands (Acne pustulosa). The former change leads, in its highest development, to Acne hypertrophica, the latter terminates in scars and the formation of double comedones. Simple Acne punctata leads, when most fully developed, eventually to the formation of sebaceous cysts; false atheromata. One must avoid describing as acne, purulent folliculitides of other origin, folliculitis after eczema, Folliculitis cachecticorum, Folliculitis varioliformis, Folliculitis necrotica, Folliculitis rosacea, and other pustular affections, Iododerma and Bromoderma pustulo-tuberosum.

The first stage of hyperkeratosis shows the horny layer thickened, neither torn nor split, and of more equal texture. The granular layer too, as a sign of slower cornification, is thickened, but the prickle layer is in most cases normal. At the mouths of the follicles there is always found, instead of a filter-like depression, a slight or more marked elevation, formed of horny lamellæ, which is caused by the pressure, from beneath, of the horny plug (Comedo). All comedones which are not in the act of being thrown off are found underneath a—thus thickened—horny layer. They are the product of a hyperkeratosis, extending from the general surface to the mouths of the follicles, and contain, in addition to horny substance, normal sebum; they are consequently in no way the result of an abnormal secretion of sebum. In the dilated follicle mouths the horny layer of the surface first extends in loose, vertical layers, which take in the middle a more horizontal direction, head of comedo, while they extend at the peri-

phery vertically along the inner surface of the follicle, mantle of the comedo. This alteration of direction in the axis of the opening is caused by the pressure of the sebaceous cells from within outwards, which meets a resistance in the horny plug, and arranges the horny lamellæ, which are vertically loosened from the sides, obliquely, and finally pushes them horizontally upwards.

As the process advances, the common exit of sebaceous gland and lanugo hair is transformed into a cylindrical or more barrel-shaped horny cyst, partly filled with sebum, which, the older it becomes, separates itself the more from its horny surroundings, as a firm bullet-like body, the comedo. The perfect comedo has always a much compressed, hard, almost always more or less blackened head, and a denser mantle substance. The character of the inner and the under end, on the contrary, varies according to the duration, and the amount of sebaceous production and growth of hair. Seldom is the comedo quite simple, and then it is usually filled with a quantity of sebum, and a number of lanugo hairs, bent, twisted, or rolled into bundles. It is usually irregularly divided by horny septa, and the divisions, which contain onion-scale-like horny flakes and sebaceous cells, along with a few hairs, lie either alongside or obliquely over each other, according to the position of the related glands and hair follicles, and according to the pressure of fatty or horny complexes, which vary with the amount of scaling in the infundibulum. If the production of sebum temporarily or completely ceases, the comedo is enclosed by horny material at its under end also, and appears, when enucleated, as a completely dry, shiny, acorn-like horny body. The very old comedones, in which glands and follicles have become atrophic, and the follicular cavity a simple horny cyst, always appear thus. But even in fresh cases of Acne punctata, we sometimes find almost all the expressed comedones of this form. But more often they are hollow underneath, and end in a soft drop of sebum, of indefinite length.

From severe and persistent pressure the comedo changes its form at its upper end, the part lying directly under the surface of the skin becoming globularly swollen, and the head, up to now partly formed of oblique and vertical horny lamellæ, is still more compressed, thinned, and horizontally placed. The comedo is then covered, at its upper end, by a tangentially running horny layer, which, however, is always distinguished by its thickness and darker colour. In these older and thicker specimens the blackening of the head almost always extends a certain distance into the interior.

The almost characteristic blackening of the upper part is, in general, proportional to the hardness, dryness, and age. That it equally attacks everything enclosed in the horny mass is best seen in the hairs verti-

cally penetrating them, which, at their under end, show the absence of colour of lanugo hairs, while in the upper part of the comedo, while otherwise normal, they sometimes present a coal-black colour, and this blackness extends through the whole thickness of the shaft, and is not limited to its surface; they look as if carbonised—one of the many proofs that the blackening of the comedo no more depends on dirt than that of other hyperkeratoses.

All clinical and histological experience contradicts this, no doubt wide-spread, but none the less superficial view. As practice teaches, the blackheads of the comedones develope underneath an uncoloured horny layer, and, still covered by it, can be caused to disappear by appropriate measures (alkalis, reducing agents), and as certainly to reappear by the opposite (acids, oxygenators), that further, they are not peculiar to dirty people, and cannot be removed by soap: histology shows us that the blackness is *not* in the horny layer, *not* in the upper lamellæ of the head of the comedo, and thus *not* in the parts in communication with the atmosphere, but that it first begins further upwards where the head of the comedo is powerfully compressed and dry, and that in long-standing cases it extends outwards to all the horny structures; that, further, the normal constituents of dirt, such as fragments of vegetable fibre, feathers, hairs of beasts, paper, stone, but especially the most important—namely, the *black* constituent of dirt, *coal dust*—are never found in the comedo, while the brownish or black colour appears to be combined with quite definite, well-characterised bodies. One must here distinguish between a diffuse yellow or brown staining of the horny structures and isolated pigment, in the form of granules and masses, which also show a yellowish-brown to coal-black colour. Only the latter could, on superficial examination, be regarded as coal; so-called dirt. Admitting that these microscopical, small scattered granules were coal, no one has any right to ascribe to them the *macroscopically* visible blackness of the head of the comedo, for they are enclosed in the inside of the head, and are much too variable and inconstant to be considered. We must examine the *diffuse pigment* which causes the *macroscopic* blackness. This gives the following result.

After treatment with agents which dissolve fat (ether, benzine, chloroform), the blackness of the head remains unchanged, as it does after treatment with diluted alkalis. Caustic alkalis dissolve a part of the colour without breaking it up, and the head of the comedo remains a trifle paler, but, as a whole, not much altered. Acetic acid, concentrated Hydrochloric acid, concentrated Nitric acid, Chlorine water, and Peroxide of Hydrogen, gradually completely remove the blackness, which is immediately removed on boiling with Chlorine water or Aqua

regia. If anyone wishes to convince himself that the blackness of an expressed comedo is not due to "dirt," *i.e.*, coal dust, he can do this, without a microscope, by boiling it in a test tube, with a little Hydrochloric and Nitric acid. The result is a yellowish white comedo, without a black head. If this is squashed out under the microscope, we still see in the inside of the head a few yellow, brown and black masses of pigment. All the yellow and brown, and a few or all the black ones disappear on treating the microscopical preparation with Aqua regia. But there often persist a few black masses and granules of the diameter of white or red blood corpuscles, whose carbonaceous nature is now decided, and may willingly be admitted.

FIG. 20.—Comedo.

H. Hair. *U.* Unblackened horny layer. *S.* Sebaceous gland.

The excessive resistance of the diffuse, yellow and brown horny colour, as well as that of the yellow and brown masses, their partial solubility in the alkalis, and finally their breaking-up with strong acids

and on oxidation, make it very probable that we are dealing with a coloured product of reduction of Keratin. In this way the darker cells and masses would represent the more degenerated or carbonised, and the quite black ones the last terminal product. That complete coaly blackness may be finally produced by this degeneration of the horny substance is shown by the black lanugo hairs of the comedo head.

It is consequently very probable that some of the black masses approach true carbon and share its resistance. They are distinguished from particles of soot by their more angular form, and the fact that, repeatedly treated on the slide with Aqua regia, they only shrink. To this miserable fragment is reduced that part of the comedo, which, as regards dirt, is still open to discussion, and it may equally well arise from the horny substance itself as from the outer world. But the less dead substances can be recognised as penetrating from without into the comedo, the more do we meet with living organisms in those horny and fatty cysts, and in the true, completely, or at least externally closed comedones; only they are of a vegetable nature.* The distinction between both kinds of bodies is clear. When the follicle is cornified, and especially when it is closed by a comedo, naturally no ordinary manipulation can cause the entrance of foreign substances. Before the setting in of hyperkeratosis, and in the spontaneous sealing or artificial squeezing out of the horny plug in washing, drying, the rubbing in of ointment, etc., a few living or dead foreign bodies may very well penetrate, against the stream of secretion, as far as the mouth of the gland, and here become encapsuled in subsequent cornification. Thus are to be explained the very rare foreign bodies found inside the comedo, such as ears of corn and an occasional true fragment of coal, the occasionally present ultramarine, etc. But single micro-organisms, reaching here in the same way, may, although not endowed with the power of movement, increase so rapidly by proliferation that they fill the whole comedo. Indeed, there could scarcely be a better protected and tempered chamber for such micro-organisms as can live on fat and horny substance, than is provided in the cavity of the comedo, and it will therefore cause less surprise, that in acne almost every comedo contains a swarm of micro-organisms, often in pure culture, than that, up to now, we should have had no suspicion of their existence. One finds them in sections and squash preparations of expressed comedones, as well as on complete sections of acne skin.

Of the micro-organisms which are very frequently found here, I

* In the stagnating secretion of dilated sebaceous glands there are often found acari; but these masses of sebum, which can be squeezed out like worms, are not comedones, and should not be so called.

would specially note the keratophilic, oat-shaped "bottle bacillus," and the diplococcus of seborrhœic eczema. Both are chiefly limited to the head and mantle of the comedo, and grow outwards in the horny fissures. Inside, on the contrary, one always meets with a special form of bacillus. This must attract most of our attention, for it is exceedingly probable that it is not only an accompaniment but the actual cause of comedo formation, and therefore of acne in general. In contrast to the other organisms mentioned, I have found these bacilli present in every comedo. Although this circumstance alone points to an etiological significance, the position in some of them is also in its favour. The bacillus always occupies the *lowest* part of the comedo and extends from here outwards, up to the mouth of the sebaceous gland and the angle of the lanugo follicle, if both are still present unchanged. If, as is often the case, several organisms fill the comedo, the others, especially the bottle bacilli and the diplococci, tend, by their position in the upper part and on the adjacent surface, to show themselves as later arrivals, while the more important bacillus occupies, in pure cultures, the centre of the base of the comedo.

But the most stringent proof of its etiological significance, so far as such can be supplied by histology, I recognise in its relation to suppuration. For, to state it at once, the secondary and non-essential suppuration in acne is not induced by an accidental contamination with pyococci, but is induced by the same organism, which, by its constant presence in the base of the comedo, may be recognised as its probable cause. To this last phase of the acne process, I will return in conclusion, after I have discussed the inflammatory changes in the acne skin around the comedo. And further statements about the bacilli will be added.

The formation of the comedo has more or less striking results on the affected follicle and on the surrounding skin. The larger, as a whole, the follicle is, and the more voluminous its sebaceous glands, the longer can the comedo exist, simply as a cystic dilatation of the duct, with the lobules of the sebaceous gland and the little appendix of the lanugo hair follicle beneath. But after some time there always developes, first in the smaller follicles, and later in the larger, a destruction of the hair follicle and the gland, in one of two different ways. Where the hair follicle is seated perpendicularly in the skin as on the nose and the ear, the prickle layer of the hair follicle, and later that of the sebaceous glands, is, through the increasing internal pressure, which tends to globularly dilate the follicle, again converted into a simple epithelial surface, and its products again assume the character of a simple horny layer. From the simple epithelial sack, which now represents the follicle, there usually runs downwards, a

short cellular process of connective tissue, which is to be regarded as analogous to the well-known cellular connective tissue process, in renewal of the hair. Or, if the follicle is oblique in the skin, the cystically dilated duct is frequently bent from the rest of the follicle, and laid alongside it, so that the hair and the sebaceous mass, running into the comedo, describe distinct spiral windings. As the comedo increases, the epithelial surface of the follicle is not directly taken up into the comedo, but rather compressed into a double-walled, flat shell, which undergoes atrophy, and finally may still be found in sections, as a fine epithelial cord, at the side of the much enlarged comedo. This also indicates the ordinary fate of the follicle in the formation of double comedo, but it is certainly not limited to this only, being frequently observed in all oblique comedones, especially of the extremities.

Very large follicles are preserved from this total destruction. But where acne lasts beyond puberty, the cystic process goes on to this extent, even in the largest follicles, and there are found remarkable horny and sebaceous cysts, of the size of a pepper-corn to that of a pea, especially on the back and neck. In some of these cases, especially when frequent mechanical irritation, such as habitual expression and squeezing of the nodules is added, these cysts develope, by the periodical collection of horny contents, into sebaceous "boils," the size of a cherry or a plum, sometimes elevated like warts, which always have a tiny external opening, and are now and again falsely described as "grit-boils" or atheromata. They are simply the extreme development of the simple dry acne process.

Still more important than these changes in the follicles, which are mostly to be attributed to mechanical factors, are the hyperplastic changes, which are regularly extended throughout acne skin, and whose existence alone proves that the acne comedo differs from the other varieties of comedo — *e.g.*, those of scars. There must be in acne some permanent irritant from the follicles, acting more or less deeply in the cutis, which induces a chronic hyperplastic inflammation. This is most developed around the follicles, and extends, in the slightest form, only to the surroundings of the cutaneous vessels and to those of the coil glands; in all severer cases the whole cutis is transformed into a very cellular tissue, which, on account of its numerous plasma and giant cells, possesses a certain superficial resemblance to tubercular tissue.

To put it more precisely, the facts, which are only clear with good protoplasm staining, are the following:—First, the connective tissue cells, on all the capillaries surrounding the follicles, and the adjacent capillaries of the superficial vascular net, increase, and, retaining their

spindle form, run together into a protoplasmic net. Then certain hypertrophic cells become rounded, withdraw their processes, develope a very powerful basophilic staining capacity and a cubical form with rounded ends, thus forming plasma cells. In other cells mitoses appear, and still others swell, with constant increase of protoplasm, to gigantic, very deeply stained cells, which are distinguished from the ordinary plasma cells only by their multipolar, sometimes even branched form, and their greater size. In addition the mast cells also increase, but usually take a simple round form. These four varieties of cells—simple hypertrophic spindle cells, enormously increased and deeply stained multipolar cells, rich in plasma, and ordinary plasma and mast cells, now surround, in almost constant proportions, the hair follicles and vessels. Around the coil glands there are rather more pure groups of plasma cells, but otherwise the plasma cells, in contrast to tubercular and syphilitic plasmomata, are usually separated from one another like mast cells; only here and there are a few capillaries surrounded by collections of plasma cells only.

As the process extends, the cell proliferation and atrophy not only becomes more extensive, but there developes, especially around the follicles, a formation of multi-nuclear cells, of giant chorio-plaques, and finally, of true giant cells, with regularly-arranged nuclei and fine reticular, acidophilic protoplasm. Still the latter are rare, while the simple protoplasmic giant cells, with unarranged nuclei and basophilic protoplasm (chorio-plaques), are very numerous. All these hypertrophic structures are seen regularly scattered among simple, swollen spindle and plasma cells. Leucocytes, on the contrary, unless artificial suppuration developes, are almost completely absent.

From other plasmomata, especially of tubercular and syphilitic nature, the hyperplastic inflammation of the cutis in acne is distinguished, in addition to its invariable culmination around the follicle, and this mixture of all kinds of cells, chiefly by the completely, or almost completely absent degeneration of these cells. There are no pale plasma cells, as in Syphilis and Tuberculosis, no broken up plasma cells, as in Mycosis fungoides; on the contrary, the purely progressive forms of multipolar spindle cells and of chorio-plaques predominate; only rarely do we see the commencement of degeneration in the formation of true giant cells. The hyperplastic inflammation in acne has therefore an almost purely progressive character.

The elastic and muscular tissues do not hypertrophy, nor does the collagenous at the commencement, but if the process last long, there appear, in place of many masses of cells, newly-formed masses of collagenous tissue. The blood vessels are, in places, especially around the follicles, much dilated. But the lymph spaces are almost everywhere

dilated, especially in relation to the areas, rich in plasma cells. The acne skin thus acquires, in many places, an almost œdematous appearance, and one understands its tendency to the formation of urticarial wheals after simple pressure; regional Urticaria factitia of acne skin.

The epithelium also participates in the general hyperplasia, although only in moderate degree. We find the normally delicate epidermic epithelium thickened, and almost always containing mitoses, and the sebaceous glands also enlarged so far as they are not transformed into comedones. The hair follicles and coil glands, on the contrary, usually show no mitosis or enlargement. The whole hyperplastic skin loses its elasticity, the enlarged follicles which do not contain comedones gape, and the normal secretion stagnates in them, and can be pressed from them, in artificial worm-form, according to the size of their mouths. These sebaceous worms have, as we have remarked above, nothing to do with the comedones.

The thus gradually induced hyperplasia of the skin next appears in areas around the follicles, and maintains, in its further extension, an irregular tuberous character. It is never so equally diffuse, and never gives origin to such grotesque deformities of the face, and especially of the nose, as the hypertrophying seborrhœic rosacea, the so-called Rhinophyma. It disappears by resorption of the cell masses, and leaves behind it a very collagenous firm cutis, with irregular surface and deep scars, due to intercurrent pustulation.

This latter, the suppuration of the follicles, is a much more frequent development in Acne punctata, than the Acne indurata just described; it is added to it, at least temporarily, in almost all cases. It is one of the most important consequences, which the better knowledge of the ordinary staphylogenic impetigo has produced, that we can certainly not attribute the suppuration of acne to the ordinary pyococci. At least they are absent in all the twenty cases of Acne punctata which I have carefully examined, while, as is well known, they are always met with in staphylogenic impetigines and furuncles. The course of the suppuration in acne is quite different to that in furuncle, so that we can distinguish histologically, with much more certainty than clinically, true furuncle from suppurating acne nodules. The difference between the causes of suppuration in the two affections could have been already concluded from the fact, that acne pustulosa has no tendency—like sycosis—to develope into general furunculosis. Indeed, it is remarkable, that the ordinary pustular affections of the skin are not often combined with acne pustulosa.

The peculiarity of the suppuration of acne, of course depends on the presence of the comedo. The bacilli, which, under certain circum-

stances, cause suppuration in acne, lie in most cases enclosed in the comedo, without displaying any pyophoric action. Especially those cases of Acne punctata, in which the comedones are completely closed on all sides, even underneath, have so thoroughly walled up the bacilli, that the pyophoric substance can no more get out than the leucocytes into the comedo. It is otherwise in the case where the process of cornification has not attained such dimensions, and fat is mixed with the horny mass. There we find the bacilli more frequently in the entrance of the follicle, the comedones are open below, and the bacilli grow readily into the fatty masses, stagnating in the ducts of the sebaceous glands, and then into the glands, and the hair follicle itself. These are the cases which are prone to suppuration.

We can therefore, as in ordinary coccal suppuration, distinguish three phases of the process: an Impetigo, a Perifolliculitis, and a Folliculitis. But they differ in that, in acne, pure folliculitis is frequent, while it is the exception in furunculosis, and that conversely, Impetigo, which almost invariably forms the first phase of the latter, appears only rarely pure, as a phase in acne. Perifolliculitis is frequent in both processes, but naturally more so in furunculosis, since, in acne, the pyophoric substance lies, not only in the follicle, but enclosed again in the comedo inside that, and the leucocytes consequently tend to collect in the follicle, around the comedo.

The bacilli are about $\frac{1}{3}$ to $\frac{1}{2}\mu$ broad, $1\frac{1}{4}$ to $1\frac{1}{2}\mu$ long,* therefore pretty small and plump. They are very often arranged in threads (up to 5μ) composed of three or four bacilli. Their main characteristic lies in their *irregular arrangement*; the collections look just like bundles of spelicans, from which some project on all sides. Consequently they show in the densest collections no regular arrangement. In the older bacilli the central part of the rods is faintly stained, while the ends show deeply-stained points. Very old collections of the bacteria, which are often found at the base of completely-closed comedones, resemble a faintly-stained, tangled net-work of threads, with many deeply-stained points. The bacilli, if they are not too old, are readily stained with basic anilin colours. In the latter case a pararosanilin-iodine method (*e.g.*, Weigert's) is to be preferred. They are completely decolourised by acids, thus differing from the smegma bacillus, apart from the great difference in size. With the methyl-blue-glycerine-ether method, we see that the rods are invariably embedded in a very faintly blue stained mucoid mass. They belong, then, to the mucus-producing bacilli.

* Many bacilli show in the centre a constriction or an unstained cross line, and there are often individual bacilli of half that length, which probably represents the true length ($\frac{5}{8}$ to $\frac{3}{4}\mu$).

In the densest collections these bacilli fill the fatty centre of the comedones, and the outer zone of the collections is usually more deeply stained than the inner. From here, individual collections extend outwards for a short distance between the flaky layers of the mantle of the comedo; the external layers are usually free from bacilli. This is the condition in Acne punctata and in the comedones, which have swollen up into spherical horny cysts.

If suppuration set in, the conditions are different, according as we are dealing with circular, closed or open comedones. In the former case the suppuration is always limited and—at least according to my preparations—invariably endo-follicular. The suppuration does not proceed from the bacilli in the comedo, but from those in the supra-comedonal horny layers. There is formed a bacillogenic impetigo, and secondary to it a slight peri-comedonal suppuration, which extends more or less deeply. The impetigo is, like all impetigenes of the hair follicle, superficial. There are no staphylococci on its covering, but only dense layers of the bacilli, just described. They lie closely surrounded by leucocytes, but apparently not in them. But there are in the leucocytic paths, extending upwards at the side of the comedo, a few wandering cells, which are dotted with bacilli. This circular suppuration around the comedo I have seen replaced in other preparations, by an emigration of white blood corpuscles dependent on diplococci. In these cases seborrhœic crusts overlaid the comedo, and there was, clinically, a combination with seborrhœic eczema. The innumerable diplococci of the crust were abundantly found in the purulent zone around the comedo, and the leucocytes there contained diplococci instead of bacilli. But here also there were no staphylococci, and consequently the pus was thin and contained much epithelium, rather representing purulent epithelial debris than pus. I found, close together, in one acne pustule, leucocytes containing bacilli and diplococci.*

If the comedo is open beneath, the suppuration, along with the growth of the bacilli, assumes much greater dimensions, for here the pyophoric products are poured freely into the lymph spaces around, and the leucocytes can advance by the same route. Here one can, in general, distinguish two types of cases, *Folliculitis pustulosa superior and inferior*, according as the suppuration begins with an impetigo, or is induced by a collection of bacilli underneath the comedo, in the hair follicle or sebaceous gland. The former is usually the case in those comedones which fill the whole lanugo hair follicle, and flatten it out,

* In the examination of acne one should always be on the look-out for the frequent combination with seborrhœic eczema, as indeed in other histological relations also, but this is not the place to discuss it.

causing it and the sebaceous gland to disappear; the latter is chiefly present in those comedones which only fill the excretory ducts of larger follicles, while beneath them hair follicle and sebaceous gland remain unchanged. Folliculitis superior shows a more or less considerable supra-comedonal mass of pus, surrounded by a peri-comedonal one. The comedo, which is now swimming in pus, becomes finally also filled with pus, and breaks up into individual horny lamellæ. Leucocytes, surrounded and permeated by bacilli, are invariably found, but there are no staphylococci. In one of my cases, a peri-follicular, unilateral suppuration, which succeeded to a laterally placed impetigo, preceded this endo-follicular suppuration of the follicle. This form also occurs, but the rule is endo-follicular suppuration; Folliculitis proper.

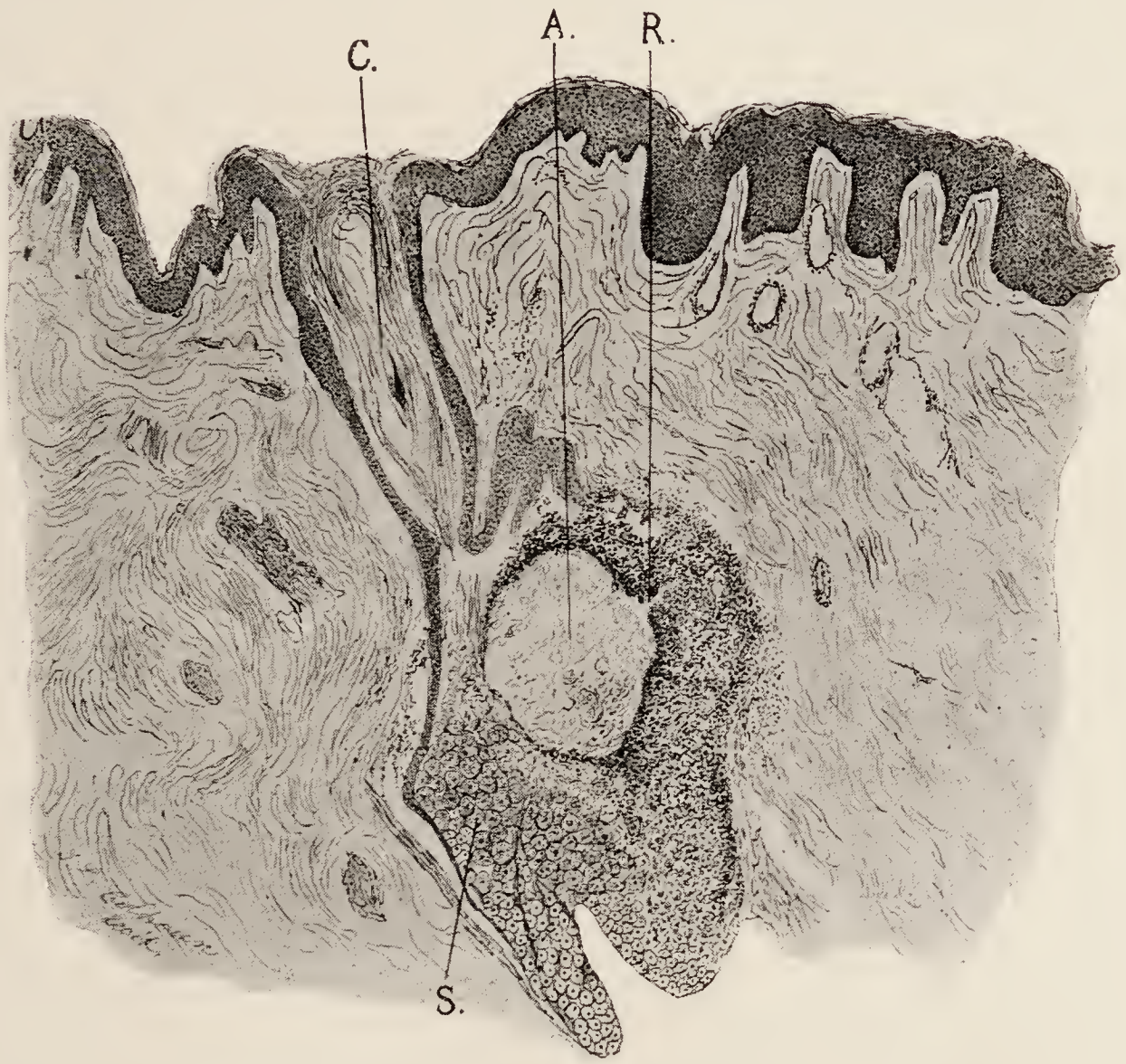

FIG. 21.—Acne pustulosa inferior.

C. Comedo. *A.* Abscess. *S.* Unaltered sebaceous cells.
R. Rupture of abscess into surrounding tissues.

Still more simple is the suppuration in Folliculitis inferior. The bacilli lie most frequently in the mouth of the gland, or in the gland itself. In the latter case the cellular structure has mostly disappeared. Here the leucocytes have a direct entrance, and so parts of the follicle may suppurate, part of the sebaceous gland, or the whole of this, or a

piece of the follicle. As the suppuration extends the leucocytes collect outside the follicle; a peri-folliculitis developes from the folliculitis. A peri-folliculitis surrounds a few of the larger hair follicles from the commencement, on account of the resistance of the follicle membrane. But it always remains slight; here also the suppuration is chiefly endo-follicular. Therefore it is that, in all follicular abscesses which are caused by acne, the abscess is margined to a much greater extent by the old follicle membrane, than in the ordinary furuncle of the hair follicle. The follicle membrane is sometimes enormously distended, and only at certain places, *e.g.* the sebaceous gland, penetrated.

And further, this general relation explains how it is that the abscesses of acne skin are always exactly limited to the follicle, and do not, like the staphylogenic suppurations, extend in diverse directions. At the most, two or more follicles, which have been hyper-dilated by the suppuration, run together, and then form a common sack of pus, which later is transformed by scar formation into the comedo duplex, triplex, etc. There are, further, in the behaviour of the micro-organisms, characteristic differences between the acne abscess and furuncle. The bacilli form, in the centre, more or less large collections, but never such compact masses and hollow cylinders as the staphylococci. But they are immediately disturbed by the entrance of the leucocytes. Sometimes they overcome them, perhaps grow in them, but for the most part they pass into the suppuration, and one must stain and search with great diligence, in order to find them. They are most numerous in the larger abscesses, around certain groups of horny cells, remains of the root sheaths, and one finds them best by examining the epithelial remains. Equally important in the diagnosis of the acne abscesses is the determination of the absence of staphylococci. Where, in the central sections of a hair follicle abscess, staphylococci are completely absent in the centre, the suspicion of an acne abscess is justified.

But even if, as is often the case, the pus drops out of the section, one can still establish the diagnosis by the close examination of the elements of the abscess wall. If layers of epithelium are evident all round, the suppuration is due to acne, and is not furuncular. If a distended epithelial membrane is absent, and a cellularly infiltrated cutis forms the margin of the abscess, there are still sufficient distinctions. I have noted above, that the cellular hyperplasia in acne is distinguished by the fact, that all the different kinds of cells appear mixed up together. This character is preserved even in suppuration, the leucocytes only permeate the mixture of other cells and form part of it. They increase in number in the neighbourhood of the abscess, but only very gradually, and thus the whole cellular zone around the abscess becomes broader, but never consists of pure pus. To an outer

segment, equally permeated by leucocytes, there succeeds, with gradual liquefaction of the collagenous tissue, a central one, which may be defined as a cellular debris, consisting of leucocytes, plasma cells, spindle cells, and chorio-plaques. Further inwards comes the internal zone, directly margining the abscess; in it leucocytes and detached epithelium predominate, and the connective tissue cells are practically absent. In the abscess of the hair follicle, produced by staphylococci, the infiltration zone is smaller, and the broken-down purulent part is more sharply defined from the non-purulent. And last of all the great number of large multi-nuclear chorio-plaques is quite characteristic of acne abscess, as opposed to Furunculosis, and is alone sufficient for the diagnosis.

Since the suppuration in acne depends on the acute outpouring of larger amounts of the same poison into the vascular connective tissue, which, with slighter and slower action, has already induced hyperplastic changes, it is not surprising that further away from the abscess the formation of large spindle cells, plasma cells, and giant cells goes on to a still greater degree. It extends, according to the greater stagnation or absorption of the poison, to a region with a diameter of two to four centimetres, rarely further, and only exceptionally does it produce infiltration of the fatty tissue. But the epithelium of the surface always participates in the hyperplasia. An unusual number of mitoses of the epithelium surround the abscess on the surface, and the epithelial ridges are, all of them, much increased in length and breadth.

The process of healing of the acne abscess is different, according as the follicle or only its contents have suppurated. In the slightest cases, only the comedo with its bacilli is thrown off, and thus, every reason for further suppuration being removed, the skin returns to the normal, and comedones may again be formed in the same follicle. With simultaneous, appropriate treatment complete healing may be induced, without any re-formation of the comedones. It is evident, then, that the removal of them is not merely a palliative assistance, but is actually to be regarded as causal therapeutics. If the follicular epithelium is, as frequently, only partly destroyed, healing may also take place without the re-formation of comedones. Only if all the follicular epithelium is destroyed, do we have simple granulation, and a deep-sunken scar in the place of the follicle. If several suppurated follicles run together in the depths of the skin, their epithelium almost always grows together, and there is formed a single larger cavity, which retracts in the scar formation, and opens with as many (two, three, and more) mouths on the surface as there were follicles. In this common barrel or sack-like cavity there are re-formed large comedones, so-called double and triple comedones. Now and again we see on their sides the atrophied

remains of the old hair follicle and sebaceous glands, opening into the common cavity.

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Folliculitis varioliformis (Acne varioliformis).

An affection, mostly limited to the hairy margin of the forehead, spreading from here to the head, rarely to the forehead and eyebrows, running an exceptionally chronic course, and frequently ending with destruction of the follicles. Two forms may be distinguished, a slight, superficial one, which heals with shallow depressions, and a severer, deeper one, which leaves depressed scars. The slighter form does not invariably pass into the severer, but both are present in every case. The individual spots are almost always pretty widely separated, though now and again they become confluent. The slighter form is evident as a papule, covered with a crust, at the entrance of a hair follicle, at first yellow, but later dry and brown, which falls off, and leaves a cornified depression. The severer form developes from the other, the crust with or without pustule formation increasing laterally; it is coloured deep brown, and underneath it takes place a necrotic softening, extending all round the follicle, and perpendicularly as far as the middle or under third of the cutis. If one removes the firm crust, it brings with it, without much bleeding, a large, greenish yellow, ragged mass. This form also ultimately heals spontaneously, the epidermis growing under the necrotic plug, but there are left behind deep depressed scars, like those of small-pox.

Histologically, also, two types may be distinguished. Of ten spots which I took from a typical case, six represented the slight (one of them an isolated recent papule in the left eyebrow), the others the severe type. Since both forms may heal by the dry method, the epidermis growing under the scab, and are only distinguished chiefly by the fact that the scab in the first place contains epithelium and exudation, and in the second the whole follicle and its surroundings in addition, I will call the first the *exfoliative* and the second the *excoriative*.

The exfoliative, the more superficial form, commences with the moderate dilatation of one or more adjacent lanugo hair follicles, and their closure on the surface by a firm scale, consisting simply of horizontal horny lamellæ, and penetrated by one or more hairs. At this stage, the cutis round about the follicle is markedly altered over a breadth sometimes double that of the follicle, by a collection of cells,

which appear in indefinite areas in the middle part of the cutis, are not specially limited to the surroundings of the vessels, and leave the papillary body relatively free. They consist of roundish, small, connective tissue cells, with relatively large nuclei and very little protoplasm, which, in the majority of cases, does *not* take up the same stain as plasma cell granules. Only in the most peripherally lying areas does one meet single small round cells, whose protoplasmic staining justifies the diagnosis, plasma cells, and beside them larger ones of the same nature, whose protoplasm is breaking up. Further, the areas contain ordinary spindle cells, and a moderate number of rounded mast cells. The main characteristic of these peri-follicular areas is the much dilated lymph spaces which penetrate the areas like a dense coarse net, and isolate the cell bodies, held together only by delicate collagenous fibres. Thus these areas acquire a certain resemblance to the cellular foci of Ulerythema centrifugum. Only here the distension of the elementary lymph spaces is still greater, while that of the lymph vessels is at this stage still unimportant. The dilatation of the blood vessels also is relatively insignificant, and sometimes altogether absent.

The follicles are, as above stated, distended, so that their form passes more or less from the cylindrical into an ovoid or sack shape, while the larger or smaller adjacent sebaceous gland usually shows no change. This distention depends on the enormous growth of a small bacillus, which in many points resembles that of acne. But the main distinction, which enables one to tell it at a glance, depends on the effect which it—in distinction to the bacillus of acne—exercises on the follicle epithelium. *No comedo is formed.* During its growth there may develope a slight desquamation, an abnormally marked cornification of the prickle layer of the hair follicle, as is shown by the horny closure of the follicle and by a scale, but never is the hyperkeratosis, and especially the epithelial after-growth, acanthosis, so great that a cylindrical horny body, encapsuling the bacilli, is formed in the follicle. The bacilli are found in more unarranged collections, distributed diffusely in the follicle, between the cast-off hairs on the one hand and the follicle epithelium on the other, and covering the horny cells in dense collections. Morphologically they are of the same length, but somewhat thicker than the acne bacilli, and have not the tendency which these have to longer growth. Single bacilli measure at most 1 to $1\frac{1}{4}\mu$ long, but are almost always slightly constricted in the middle, and no doubt are to be regarded as diplo-bacilli, just before division. The breadth is about $\frac{1}{3}\mu$, so that recently divided bacilli appear very plump. Three and four individuals in the form of longer threads are only rarely found, and they are very rarely bent.

This property of forming finer, longer, and slightly-bent bacillary threads gives to the large collections of acne bacilli, in contrast to the bacilli of Folliculitis varioliformis, a more spar-like feathery appearance, while the collections of the latter are denser and rounder. But both varieties are, morphologically as well as tinctorially, very similar. Both take up basic anilin colours readily; they resist iodine, but not acids.

At this early stage we only rarely meet papules already carrying a well-formed scale; we oftener see, around older spots, the, as yet macroscopically unaffected follicles distended by a growth of bacilli and surrounded by one of cells. But very soon there is added a new factor, a formation of crusts, and this is, according to all histological evidence, apparently *not* caused by the growth of bacilli in the interior of the follicle, but by the development of the diplococci of seborrhœic eczema in the scale. With this, both the histological and the clinical appearances are immediately altered.

The diplococci are first limited to the openings in the scales, where the hairs penetrate them, filling and dilating them by their large, granular colonies, while their further lateral penetration into the firm scale, is evidently not so easy. As these increase in number the bacilli in the interior of the follicle diminish. When the diplococci have taken possession of the scale, only a few faintly-stained bacilli are seen lying about the hair shaft. But the scene rapidly changes, and the diplococci induce, here as everywhere else, a sero-fibrinous inflammation with emigration of relatively few leucocytes. This exudation elevates the firm scale, dilates the mouth of the hair follicle, and presses upwards the epidermis surrounding it. Clinically, the scale now has the appearance of a crust, and if exudation is rapid, occasionally that of a bulla, elevating the scales. The firmness of the scale delays the exudation on the surface and the elevation of the scale, and so the epidermis at the side of the follicle is always extended more and more downwards, until a balance and an arrest of the exudation is produced. The exudation, coagulated in the form of a bi-convex lens, is not always placed directly above the opening of the follicle, but more frequently to one side, so that the follicle, from which the crust formation started, is often found at its border. *Several adjacent follicles may carry a common seborrhœic crust*, and on the other hand, under, for example, a crust the size of a pepper-corn, we may find, among the diseased follicles, here and there a healthy one. Since the epidermis at the side of the follicle is pressed outwards by exudation, the normal small filter is so much dilated, that almost the whole upper half of the follicle is taken up by it. On a central section through the hair follicle we consequently see in the centre, the hair, surrounded

in its upper part by a cultivation of bacilli, and then by a few layers of horny cells, and this cylinder enclosed by a funnel-shaped, fibrinous exudation with its apex upwards, containing many leucocytes, and passing above gradually into the original firm scale, which still covers the whole spot. This is, in the upper part, permeated by a number of diplococci, and these extend outwards, partly in the hair fissures, but to a limited extent also in the exudation, which has deeply excavated the infundibulum. On the a-symmetrically placed crust just referred to, it is very easy to see that the diplococci do not equally permeate the whole crust, but especially attack the hair follicles which are filled with bacilli, so that the horny substance here present is evidently to be regarded as a medium which they specially select. A little further and we meet crusted papules covered with crusts, where the diplococci have penetrated into the interior hollow cylinder of the hair, and have partly or completely taken the place of the bacilli. There are still usually found a few faintly stained bacilli in the immediate neighbourhood of remains of the hair, or an isolated colony at the base of the saccular follicle. As our experience otherwise is that the diplococci of seborrhœic eczema always prefer to remain on the surface, while in cultures they are aërobic, the tendency which they here show to penetrate deep down, inside and outside the hair, and that in an unusually luxuriant fashion, is a further proof that here they find a specially good soil, and this can evidently only be provided by the previous invasion of bacilli.

In connection with this secondary growth of cocci outwards, leucocytes now appear around the hair follicle and wander into the crust. The dilatation of the lymph spaces in the perifollicular cellular areas continues to increase, while new cellular areas are no longer formed. Then the papule sinks in again, the elevation of the horny layer as flattened down, and the crust lies on the level of the skin.

If the process is now arrested, it may immediately heal with throwing off of the crust. This occurs in the slighter forms of the disease, in which the bacillary invasion is directly replaced by the coccal growth. There remains only, at the apex of the papule or at its side, a small depression, clothed with surface epithelium, into which one or more hair follicles open; this also, in time, may be almost completely flattened out.

But the course of the affection is otherwise, if the cocci do not reach the bacilli in the hair follicle, but extend more and more laterally in the crust. Then, under the pressure of new exudation, the epithelial layer round about the follicle gradually ruptures, and the crust extends outwards, directly into a perifollicular, sero-fibrinous exudation, which softens the whole surroundings of the follicle and

obliterates their structure. This penetration has a certain resemblance to the penetration of purulent exudation through the epithelial base, in the transformation of Impetigo into Furuncle. As a fact, the diplococci advance, contrary to their ordinary habits, against the stream of the exudation, and appear at the base of the hair follicle among its bacilli, so that in preparations the bacilli may be seen above the diplococci.

Now the exudation has reached its maximum. One or several neighbouring follicles are embedded in a common, sero-saturated cutis, filled with leucocytes, and the remains of connective tissue cells, in which all structure is gradually lost. This disappearance of the form of the cells is first limited, and then becomes general ; protoplasm and intercellular substance pass, without any margin, into a necrotic mass, no longer taking basic stains, and filled with all sorts of broken-up nuclei ; we have to do then, not with a coagulation necrosis, but with a gradually developing simple necrosis of the saturated connective tissue. Therefore there is no sharp margining of the necrotic tissue, no line of demarcation, but a gradual passage from inflammatory hyperplastic into dead tissue, as in ulcerating tubercular or syphilitic nodes.

It is certainly remarkable that only this enormous emigration of diplococci can be made responsible for the necrosis ; for, as a rule, the action of these organisms is limited to a superficial inflammation and the attraction of a sero-fibrinous exudation. These facts, combined with the unusually deep entrance, mentioned above, no doubt lead us to suspect that the diplococci, here present, are other than the ordinary seborrhœic diplococci. But the morphological, very characteristic indications exclude, I think, this suspicion, and we must then assume that the unusually favourable soil, and the consequent specially luxuriant proliferation of the diplococci induce the more anaërobic growth and slowly bring about the necrosis. Even staphylococci produce sometimes only suppuration, sometimes necrosis of the tissue. To the bacilli alone the necrosis cannot very well be ascribed, for they are always found inside the remains of the hair follicle, and not, like the diplococci, in the middle of the necrotic tissue ; but they evidently have a share in it, by preparing the ground for the growth of the diplococci, and transforming the surroundings into an infiltrated, only slightly protoplasmic, œdematous tissue. It may be months before this ragged necrotic tissue is thrown off, and this takes place, not by a re-active inflammation, but by its sequestration ; young epithelium slowly extending along the margin between inflamed and necrotic tissue, under the scab. Since, to do this, it must descend deeply, even to half the depth of the cutis, there result, in spontaneous healing, very deep, pock-

like scars and furrows. Artificial healing may arrest the formation of those scars, even in the period of necrosis, by inducing, instead of the deep cornification, healthy granulations, which restore the level of the skin.

Vertical sections through the necrotic mass still show, on the surface, the dense, horizontal horny scale, with its masses and packets of diplococci, then a broad zone of fibrinous exudation, which is in many places permeated by diplococci, and finally, underneath, the necrotic zone, which encloses remains of the simple dropsical tissue, and, in particular, the swollen or necrotic, but still recognisable remains of one, or usually several hair follicles. In these one still sees, here and there, small colonies of bacilli.

The whole histology of the affection is consequently a valuable confirmation of the clinical development, and, at the same time, a splendid example of a mixed infection, in the sense, that the second infection leads to spontaneous healing of the first. In the slighter form of the disease, the diplococci simply cause the formation of a sero-fibrinous crust, whose peculiarity consists in its development underneath the unyielding scale; with the disappearance of the bacilli, under the influence of the cocci penetrating into the hair follicle, whole affection disappears, with the exfoliation of a deep crust. But where the diplococci do not penetrate directly into the hair follicle, where the bacilli vegetate undisturbed, then the diplococci find other, but more dangerous methods, outside the hair follicle, of eliminating the bacilli. By their active development in the depths of the tissue they lead to its death, and the scab, which is thrown off, contains the necrosed follicle, embedded in necrotic tissue.

In both cases the affection represents a double infection, and its progress towards healing, although very, very slow, depends in both cases on the victory of the second infection over the first.

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Folliculitis necrotica (Boeck).

This affection begins with a whitish-yellow, œdematous, waxy-looking papule, corresponding to a hair follicle, on whose periphery a number of minute hæmorrhagic points form a faint violet spot. This colour is more evident, when the papules reach the size of peas, and enclose several follicles. First the centre, and then the whole papule, sinks in and forms a well-defined, hard patch, of a brownish violet, and finally of a brown colour. This is as tough as parchment, and comprises the epidermis and part of the also mummified cutis. The epi-

dermis grows spontaneously underneath it, and after the crust falls off, deep losses of substance remain. The disease affects, in addition to the forehead, the breast, neck, back, and upper-arms. Fresh outbreaks are localised in the old scars.

Boeck's examination of his case showed hyperplasia of the epidermis, especially of the prickle layer of the hair follicle, which penetrated into the cutis as a broad cone, and was distinctly margined from it. The prickle cells were indistinct in their outline, and sometimes showed no nuclei. The papilla was structureless, and contained much dilated vessels and extravasations. The vessels in the cutis were distended with blood, and surrounded by a broad sheath of hyalin exudation, especially in the neighbourhood of the follicle. Collagenous and elastic fibres were well preserved. Under this necrotic layer was a layer of granulation, and under that, sequestrating the scab, young epidermis.

Boeck lays no great weight on the fungi; but notes particularly, large packets of cocci; underneath, in the hair follicle, bacteria; and further, staphylococci and small streptococci around the hair, and very small spores of mould fungi.

Whether the dry mummification developes from stagnation, coagulation or the growth of the bacteria, Boeck does not state.

According to Boeck's description it is quite clear that his Acne necrotica is not identical with the ordinary Folliculitis varioliformis of the forehead; so much is clear from the clinical description. In it especially the blood vessels are not distended with blood, and their surroundings show no hæmorrhagic infarctions. But the two varieties are evidently closely related.

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Sycosis Staphylogenes.

By sycosis has long been understood, the purulent inflammation of those hair follicles which contain short thick hairs, as those of the beard, the pubis, axillæ, the eyebrows and eyelashes. Bockhart first recognised that this form of purulent inflammation had the same etiology as Staphylogenic impetigo and Furunculosis. Staphylogenic sycosis is rarely primary; it is usually secondary and a mixed infection. In the former cases it is almost always the result of the inoculation by the razor of an impetigo pustule over all the hairs of the beard. The spots then represent impetigo pustules of the hair follicle necks, which appear and run a completely isolated course. Much more frequently the sycosis is secondary, often to a chronic catarrh of the nasal mucous membrane,

and is then limited to the upper lip, beneath the nostrils. In another series of cases it appears in connection with seborrhœic eczema of the face, and then in irregularly margined spots in the beard or eyebrows, much more rarely in the other localities named. The sharp limitation of this secondary form is lost if the hairs of the region are regularly shaved. From the primary cases of Sycosis they are further distinguished, by the appearances of inflammation of the inter-follicular skin (scales, sero-fibrinous crusts, hyperæmia). Subnasal Sycosis especially, frequently shows such a severe inter-follicular œdema, that the appearance of "raspberry" growth developes. On epilation the root sheath is very much swollen, and a drop of pus exudes. But the majority of the hair follicles of the affected region, which contain no pus, also shows the root sheath of the epilated hair swollen, glassy or milk-white, up to a definite distance, where the change usually abruptly ceases.

Histologically, it is well to distinguish four stages of Sycosis; two superficial and two infiltrating. The first is an impetigo of the hair follicle neck, which is distinguished from the impetigo of the lanugo follicle, by the fact that it is flatter and more pointed, and remains much smaller. It has a tent-like form around the hair, and is not semi-spherically rounded. The second stage represents the nodular perifolliculitis of the follicle neck, an inflammatory, firm, painful, but not deeply extending nodule at the mouth of the hair follicle, which every pustule has at its apex.

The third stage is best regarded as a perifollicular furuncle or a perifollicular abscess. In it there are indeed complete suppurations in the cutis, but at first, only at the side of the follicle. From these three stages complete restitution is always possible. The fourth stage is that of total suppuration of the hair follicle, the follicular abscess, which naturally always ends with loss of hair and the formation of a scar.

In the first stage the Sycosis is scarcely distinguishable from the impetigo pustule of the small lanugo hair follicle. The covering is only slightly elevated, and consists of the horny layer, while the base of the pustule is originally formed from prickle layer, but is usually re-covered by a thin layer of horny cells. The healing of the impetigo pustule, even on the necks of the thicker hairs, clothed with thick horny layer, takes place very easily. The pustule itself forms a ring-formed sinus, for it is penetrated by the hair. The hair, covered by the horny layer, stretches through it, and the horny layer presents a very suitable soil for the pyococci. At this stage the appearances in the cutis are very slight, and almost the same as those in folliculitis of the lanugo hairs. The adjacent papillæ are somewhat swollen and œdematous, and, in combination with a swelling and slight proliferation of the neighbouring epithelial ridges, these changes induce a slight, cushion-like swelling, at the mouth of the follicle. At this stage

the cocci are only to be found in the impetigo pustule, usually closely arranged around the hair; they are more rarely distributed under the cover of the pustule.

The second stage, that in which the coccogenic sycosis longest persists and is most frequent, begins with the growth of the cocci into the neck of the follicle, along the hair fissure, as far as the opening of the sebaceous gland. The collections of leucocytes follow this invasion, only as far as the limited power of distension of the neck of the follicle permits, and this is dilated into a more globular cavity, most of which is sunken in the skin. Then the collection of pus stagnates in the hair follicle, and further chemotactic action only results in the leucocytes assembling themselves in the connective tissue outside, around the neck of the follicle. Here, there is further a very marked growth of all the connective tissue cells, so that the collagenous tissue is permeated by a very large, swollen net of proliferating connective tissue cells. In the consequently dilated lymph spaces, the leucocytes from all sides approach the chemotactic spring in the hair follicle, without anywhere collecting in excessive quantity, consequently without forming an abscess and leading to liquefaction of the collagenous tissue. Therefore staphylogenic perifolliculitis, at this stage, is a firm nodule, lying superficially in the skin, crowned by a small impetigo pustule, and possibly corresponding to Besnier's Angiofolliculitis.

The further spread of the process is not usually deep, but broad. A few cocci get out of the hair follicle neck under the surrounding horny layer, and there develope single or ring-formed, communicating impetigines, at first of microscopical size, but soon becoming visible round the follicle mouth. The attracted leucocytes also fill that part of the papillary body lying beneath, and induce liquefaction of the tissue. The result is the penetration of the coccal, epidermoidal abscess into the abscess-like infiltrated and liquefied cutis tissue, which is, however, still free from cocci, and the consequent formation of a true perifollicular cutaneous abscess, at one or more places, on the side of the hair follicle. It is exactly the same process as in the formation of a furuncle from a common impetigo pustule, only it is limited to the immediate surroundings of a large hair follicle. Only when in further increase new circumscribed areas of pus are added outside, and especially beneath the purulent perifolliculitis, does their concentric arrangement around a hair follicle and the hair give them, clinically, the character of a uniform area of inflammation, which, strictly speaking, is as little seen in them as in most furuncular processes. The rule is, that a series of microscopical impetigines and furuncles are grouped around the hair follicle, before that itself goes on to suppuration, and

the explanation of this appearance is evidently to be sought in the firm follicle membrane and the high intra-follicular pressure.

The sycotic process only rarely reaches the fourth stage, and only after long existence and the addition of the accidental causes of inflammation, such as certain methods of treatment. Then there collect all around the hair follicle, such a number of leucocytes, that it almost swims in a cylindrical abscess. Inside, the cocci grow outwards between the root sheath and the prickle layer of the hair, and then begins the saturation with leucocytes of the prickle layers of the follicle and the sebaceous gland, under which the formation of hair sheaths appears to be completely obliterated. Suppuration only ends with the throwing off of the unrecognisable remains of the hair follicle and the necrotic surroundings, and with the formation of a scar.

During this, first perifollicular and then follicular abscess formation, slighter inflammatory conditions are developed further from the hair follicle, through the whole depth of the cutis. The spindle cells are enlarged, everywhere distinctly connected by their processes, and now and again accompanied by a few plasma cells. Leucocytes lie singly or in small collections in the dilated lymph spaces, being more numerous nearer the follicle. The collagenous tissue, however, is rather swollen and broadened than diminished in volume. The formation of actual abscesses with liquefaction of the collagenous tissue, begins first in the neighbourhood of the hair follicle. Here, in addition, the papillæ are much swollen, œdematous, transparent, and relatively poor in leucocytes, and the enlarged epithelial ridges between them are compressed. The epithelium, in the immediate neighbourhood of the hair follicle, is swollen and œdematous, and contains a moderate number of leucocytes; further away there are mitoses, and there is evidently, round about the affected hair, a persistent epithelial proliferation.

Around the suppurating hair follicle there is consequently found a very broad zone of serous inflammation, which is usually accompanied by great œdema. The enclosed follicles participate in this œdema and show a swelling of the root sheath, even in those hairs whose follicles contain no pyococci. It is, therefore, evident that the epilation of such hairs can have no therapeutic value. Where the hairs are closely arranged, as on the moustache, the œdema of the papillary body often leads to large, transparent, red swellings, which, constricted at the follicle necks, take a granular, "raspberry" appearance. The coil glands and the fatty tissue only rarely share in the suppuration; but they also are always surrounded and permeated by œdema and leucocytes; the spindle cells between them are swollen, and here and there plasma cells appear. Only in the rare cases, in which the

formation of larger abscesses is added to sycosis, does the fatty tissue suppurate.

From the hyphogenic sycosis the staphylogenic is so distinct in every point of development, that, from the histological side, the clinical resemblance must be regarded as a very superficial one (compare its histology). But since there also, pyococci may come secondarily into play, we may review their distribution in the staphylogenic sycosis, as found in the different stages of that process. There is always a large collection in the hair follicle neck, in the form of a collar round the hair, which is closely encapsuled by horny cells. Where pus is found in the cutis, there are almost invariably found in the neighbourhood of the hair follicle neck a number of collections of cocci in more or less large impetigenes, and, in connection with these, colonies, which may be followed into the middle of the cutaneous abscess, and sometimes into the hypoderm. In such wide extension of the process one usually finds the cocci also in the interior of the hair follicle, as far as, and even further than the mouth of the sebaceous gland, but there is no definite rule for this. But in total suppuration of the follicle they have a very regular distribution. Thick, tightly packed, hollow cylinders, filling the hair fissure, then occupy the centre of the follicular abscess, and one finds, with the same regularity, on the under margin of the abscess, somewhat deeper than the previous position of the hair papilla, a series of colonies, which are extended horizontally, parallel to the surface of the skin. From here the cocci usually extend laterally into the neighbouring hypoderm. What it is that favours this collection and horizontal spread, at the under margin of the abscess, I have not been able to discover, but it is almost constant in my preparations.

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Folliculitis Staphylogenes.

Although we possess already, in the word "Sycosis," an accepted name for inflammations of the hair follicle, we cannot give up that of folliculitis in the staphylogenic infections. Since I adopt the definition of Sycosis as an inflammation of those hair follicles only, which contain thick and short hairs (beard, eyebrows, genitals, etc.), I understand by Folliculitis staphylogenes, shortly, the purulent inflammation of the downy hairs. (The purulent staphylogenic inflammation of the long hairs of the head is a rare occurrence, which is not further considered here, being rather related to sycosis of the beard hairs.) Staphylogenic folliculitis of the downy hairs runs the same course as the impetigo

pustule, which is penetrated by a lanugo hair. But the inflammatory halo is greater, and the base of the pustule harder than in the simple impetigenes. The importance of Folliculitis staphylogenes depends on its almost invariable development into Furunculosis.

Sections through a suppurated lanugo hair follicle show a small impetigo pustule, still persisting or already dried up into a crust, which extends directly into a cutaneous abscess. It never extends beyond the border of the cutis proper, where the folliculitis has not yet led to a further furuncular inflammation, but it far exceeds the lanugo hair follicle in all directions; it is in all cases a purulent perifolliculitis, which, as the method of development shows, directly follows on impetigo, and goes on further into folliculitis. Here lies the chief distinction between this folliculitis and staphylogenic sycosis. While, in the latter, the process is arrested in most cases at the stage of superficial dry perifolliculitis (Besnier's Angiofolliculitis) or of deeper purulent folliculitis, and such appearances are accordingly to be regarded as the typical ones, we meet in the folliculitis of the lanugo hairs the earliest commencement, either as an appendix of an impetigo pustule or already as the terminal result, the cutaneous abscess, a combination of purulent perifolliculitis and folliculitis.

The latter has in general the form of a short, squat bottle, whose neck corresponds with the border between the epidermis and the cutis. According to the size of the original impetigo this communication between the epidermic and the cutaneous abscess is larger or smaller, sometimes it is merely suggested by a slight constriction, sometimes it is altogether absent, and then the follicular abscess has a short cylindrical form and reaches from the horny layer, perpendicularly or somewhat obliquely, as far as the middle or the under half of the cutis. Inside this abscess, which is everywhere sharply marked off from the surroundings, there are no further differences to be observed, everything seems to consist of pus corpuscles. Only in central sections does one always find a suggestion of the hair and root sheath in the form of a pale cylinder. The prickle layer of the hair follicle is, however, as much saturated by the pus as the sebaceous gland and the follicle membrane, and the structure of all these parts is perfectly unrecognisable.

And yet there is a simple characteristic sign of the folliculitides which, even in this stage, permits of a definite diagnosis, and especially of the separation of these hair follicle abscesses from the simple, but rare, pure impetigenous furuncles of the skin, and from those furuncles which have only used the hair follicle as a means of reaching the surface. This indicator is all the more valuable, as it brings before us directly the cause of the folliculitis; it is the shape of the collections

of staphylococci. These assume, in their downward progress, the form of broad, hollow cylinders, which grow between the hair and the follicular epithelium, just as the cocci of impetigo do between the horny and prickle layers. It is the hair fissure, frequently referred to, which, expanded and dilated by cocci, gives them the form of thick, hollow cylinders. Wherever such a cylindrical structure is visible, standing perpendicularly or obliquely to the surface in the centre of a cutaneous abscess, we have to do with a folliculitis; moreover, I have never missed this coccal cylinder in folliculitis; it is practically pathognomonic. Of course, for its recognition, good differential staining is required. Where the coccal cylinder is absent, the cocci irregularly distributed, but the structure otherwise resembling that of a cutaneous abscess, we have to do with the direct penetration of the impetigo into the cutis, without the mediation of the lanugo hair follicle, with the rare "impetigenous furuncle." If the follicle is only secondarily affected beneath, and only serves as a method of escape for the pus to the surface, we always find it a-symmetrically and almost never completely suppurated, and the cocci sparingly and irregularly distributed in it. This indicator I found very valuable in the examination of a follicular abscess of the skin, which, on account of its development during pyæmia, had aroused the suspicion of an embolic origin. It proved to be only a feebly developed impetigo pustule, over which the horny layer was permeated with pyococci. This circumstance alone made it very probable that the cocci had penetrated from the surface into the skin, as is the case in all impetigines. But a surer proof that we were dealing with an outward infection, and especially with follicular abscess formation, was found in the presence of rectilinear, cylindrical masses of cocci, which occupied an almost perpendicular position in the centre of the abscess.

Trichophytosis.

Trichophytosis is the common name for a whole series of mould fungus diseases of the skin, which individually present great differences, but all possess in common—(1) that they induce a scaly disease of the surface epithelium, (2) a disease of the hair, leading to destruction or at least to the dropping off of the hair shaft, but on the contrary, (3) do not lead to the formation of scutula. This last point distinguishes the group of Trichophytosis from that of Favus, the second from a series of other fungus diseases of the skin (Pityriasis versicolor, Tinea imbricata, etc.), the first from certain diseases of the hair shaft alone.

The differences between individual Trichophyta are related, on the one hand, to the greater or less effect on the epidermis and the hairs,

which vary from simple scaling up to vesicle and crust formation, from a scarcely detectable change of colour up to splitting and dropping off of the hair, to the slighter or more severe implication of the cutis in the inflammatory process, from slight erythema up to tumour formation, and finally, to the nature of the topographic extension, in that, in some cases, only the hairy scalp (in children), in others only the beard, in still others the skin where covered with lanugo hairs, and finally one or two of these localities may be simultaneously affected. On account of the *incorrect* view, that there was only one form of Trichophyton, the difference in the individual forms was chiefly ascribed only to *topographical* distinction, and a Trichophytosis capitis was distinguished from a Trichophytosis barbæ (Sycosis hyphogenes), the same cause being ascribed to all these forms. But in view of the clinical fact of definite geographical differences—such as the predominance of Trichophytosis capitis in London, Trichophytosis barbæ in Paris and North Germany, Trichophytosis corporis in Vienna—it suggests itself that *etiological* differences may lie at the root of these topographical differences, and this speculation has recently become a certainty by the discovery of a *series of different trichophytic fungi.*

Time will show how far the difference of the trichophyton fungi is due to topographical extension, or whether—which is clinically scarcely probable—all trichophyta can flourish without distinction on the different soils of different parts of the skin. As yet I can only say with certainty that one definite Trichophyton, the Trichophyton oïdiophoron—which I cultivated pure from the case of "Peter," following it in all its phases—induced in the face a scaling erythema, and, a few weeks later, the nodular form of hyphogenic Sycosis. Since this is the normal result in the beard, although scaling erythema with threads of fungus in the scales, which does not lead to nodular Sycosis, also occurs, it is pretty clear that the two clinical appearances of Trichophytosis corporis and Trichoph. barbæ can be induced by one and the same organism. The same is true—*mutatis mutandis*—of a group of trichophytic fungi of the head, which can both lead to scaling of the spots and to the nodular Trichophytosis of the scalp, the so-called "Kerion." Others are as definitely limited to definite localities, *e.g.*, the heads of children, the bare skin of adults, and so on.

This being so, and since we are not yet in a position clearly to indicate the relation between the forms of the disease and the existence of individual species of Trichophyton, our anatomical interest is chiefly restricted to illustrating, by typical examples, the three grades of intensity of the trichophytic affection; the *erythema*, the *vesicles* and *crusts*, and the *nodes.*

The fourth and highest power of a trichophyton fungus, that of

growing into the cutis, is such an uncommon occurrence that we must hesitate before hastily enrolling such a fungus in the otherwise well-characterised group of trichophytic fungi. It most probably belongs to quite another species, to which some other name should be given. The existence of a Trichophytia dermica (Campana, Bonome) is consequently still problematical.

The case of Peter may serve as an example, both of the erythematous and nodular form of trichophytosis :—

> The patient, æt. 50, felt an unusual itching in the beard, in the beginning of December 1891. Eight days later the skin was reddened in different parts of the beard, and in the course of four days the erythema extended over a region of the under part of the neck, as broad as the palm of the hand. It consisted of polycyclical, confluent, erythematous spots, *which had a somewhat elevated, bluish red border*, about one centimetre *broad*, on which there were *small vesicles* and *crusts*, and here and there fine scales. The centre of the spots was somewhat depressed as compared to the border, of a yellow colour, and slightly scaling. On the affected area the beard hairs had *partly fallen out*, those which remained showed *no striking changes ; stumps of hairs were not found.* These scales and hairs showed the presence of a fungus. On cultivation the hairs produced a pure culture of *Trichophyton oïdiophoron.* Sections from the border of the affection showed the threads in the horny layer and in the hair fissure.
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> The affection was healed in the course of a week by chrysarobin, and apparently remained healed for fourteen days ; but there then appeared, at certain spots on the previously affected area, firm nodules, the size of peas or more, in relation to the hair follicles. At first they were scattered over the whole region of the beard, then nodules and nodes ran together. In particular, the region under the chin was very much affected with nodules. The hairs, again, produced only pure cultures of the same Trichophyton. Under treatment with mercury-carbolic-plaster muslin the nodules softened, and gave exit to some pus ; others were flattened out, and after the lapse of several weeks the nodular form of the hyphogenic sycosis was definitely healed. In excised pieces of skin the fungus appeared only in relation to the hair follicles.
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> In the interval a grandson of the patient, who slept in the same bed with him, developed a trichophytosis of the hairy scalp, from which the same fungus was cultivated. The areas in this case were distinguished by the fact that the hairs fell out, but did not break off and leave stumps. And, lastly, a son of the patient, nineteen years of age, developed a few spots of Trichophytosis at the anterior and posterior borders of the scalp.

Sections taken from the erythematous border of the first stage showed the Trichophyton, both in the horny layer in the form of mycelium, running slightly bent but rarely branched, and in all the hair follicles which it came across. In these the fungus threads grew outwards in the hair fissure, at first between the cuticle of the hair and the horny layer, and later between that and the cuticle of the root sheath, or even inside the latter. The fungus threads dilated the pre-existing fissure between the two epidermic layers, and loosened the hair in its sheaths, but always remained separated from it, as from the

prickle layer of the hair follicle, by cornified and cornifying layers of cells. Where the hair was removed in making the section, there was seen, at the base of the hair follicle, the smooth, hollow cylinder, covered by the cuticle of the root sheath, and ornamented with threads running parallel from above downward, which only here and there sent out horizontal, bent, lateral branches. Their breadth varied very much — with methyl-blue protoplasm staining, $1\frac{1}{4}$ to $2\frac{1}{2}\mu$; with gentian violet-iodine staining of the fungus, and co-staining of the fungus membrane, $1\frac{1}{2}$ to 3μ; but still more did the length of the individual cells, namely, from 2 to 16μ. The breadth of the septa was 1 to 2μ. Cross sections of the hair showed that the threads, especially underneath, penetrate between the individual layers of the root sheath, and surround their cells with branching processes. But there is never a breaking down into oïdia; the very frequent short septa should not (with protoplasm staining) be confounded with that.

The reaction of the skin to this invasion of fungus is shown, not only in the dilatation of all the blood vessels, but as the clinical appearance suggests, in a hyperplasia of all the cellular elements, both of the epidermis and the cutis. The ridge system of the former is broadened and deepened, and everywhere shows mitosis. The connective tissue cells also, in the cutis, are much more numerous than usual, especially around the papillary vessels and the hair follicles, less so in the rest of the cutis. Sometimes the dilated capillaries have a broad mantle of cells. All the connective tissue cells are increased in size, rich in protoplasm, and some of them show mitosis. But the hyperplasia never goes on to the formation of plasma cells, nor is there anywhere a noteworthy emigration of leucocytes. The skin presents the type of a simple inflammatory hyperplasia. Consequently the lymph spaces are, in general, somewhat enlarged, but the collagenous and elastic tissue is normal.

From the second, nodular period of the same case I have two pieces of skin. The first, representing the acme of the process, shows that the hyphæ on the surface have disappeared or degenerated into almost unrecognisable angular rudiments; those of the hair follicle, on the contrary, have all broken down into almost cubical, or short, cylindrical, angled, rarely rounded oïdia, which are still partly arranged in rows. They lie, chiefly packed together in the much dilated hair fissure, between the two outer layers, mixed with collections of secondarily immigrated eczema diplococci. But, in parts, the fungus, breaking through the root sheath in different places, grows into the hair shaft, and presents itself there, sometimes still as hyphæ, sometimes already broken down into oïdia. During this further development of the fungus there go on very definite, purely progressive changes,

which may be shortly characterised as the formation of a *wide-spread plasmoma.* One rarely finds the plasma cells so regularly distributed through the skin as here. In relation to the deep lying cause in the hair follicle, the underlying part of the cutis in particular, and a part of the hypoderm are the seat of a very dense growth of cells, by which the under part of the hair follicles, the coil glands, and a part of the fatty tissue, run together into a uniform mass of cells. No special arrangement round the vessels is recognisable, the cell masses are only here and there separated by thicker collagenous fibres and the unaffected cutaneous muscles. The upper part of the cutis shows, in place of this continuous plasmoma, a much more sparing, areated, the free inter-spaces a simple but very active hyperplasia of the connective tissue cells, but no hypertrophy of the collagenous tissue. The hypertrophy of the epithelium has advanced still further. Numbers of mitoses are found; the epithelial ridges are partly represented by thick plates. In view of this general cellular hypertrophy, it is rather remarkable that the mast cells are not increased in number.

But the process does not end with the formation of extensive masses of plasma cells. In the middle of the cell masses a number of chorio-plaques are formed, especially in the under part of the cutis. They are of the most varied size and form, contain very many nuclei, and the largest ones show a diminished staining of the protoplasm, though not so great that one can describe them as giant cells. They usually lie together in collections, and here, and only here, there is sometimes a collection of leucocytes, a small, purulent-looking area in the middle of the cell mass. The blood vessels are everywhere dilated, as are the lymph spaces and vessels, especially in the papillary body. This, and the absence of collagenous hypertrophy explains the doughy consistency of the nodes, which in certain parts of the surface give the impression of œdema.

The second node showed the resorption and softening under the treatment with mercury-carbolic-plaster muslin. Here the fungi on the surface and in the follicles of most of the thrown off hairs have disappeared. A general moderate emigration of leucocytes permeates the epithelium, and all parts of the cutis, especially the collections of plasma cells, which are reduced, partly by simple atrophy of the cells, and partly by the removal of whole cells, leaving behind very wide lymph spaces. The hypertrophy of the spindle cells is everywhere retrograde, and there remain only the islands of rarefied cells in place of the diffuse plasmoma. That the moderate local leucocytosis, which sets in towards the close, is not due to the mercury, but probably usually accompanies the death of the hyphomycetes, the following case of artificial Trichophytosis teaches us, and it further gives the oppor-

tunity of becoming acquainted with the form of the trichophytic vesicles and crusts.

> Dr Neebe inoculated his leg with *Trichophyton oïdiophoron*. On the thirteenth day redness and swelling formed around three hair follicles, ran together and extended peripherally, with severe itching and the formation of vesicles, and on the eighteenth day presented a circular spot, the size of a sixpence, sunken in the centre and showing small clear vesicles on the two mm. broad, one mm. high wall.

Verticle sections show, in the middle, a thick fibrinous crust, surrounded by one or several vesicles with serous or fibrinous contents; the ends of the section lie in healthy tissue, so that one can follow the rise and fall of the acute inflammatory process. Where this culminates underneath the lateral vesicles, the superficial vessels are greatly dilated, and surrounded by the same hyperplastic cellular material, as in the previous cases. The epithelium also has proliferated and is pressed downwards by the bleb. There is no leucocytic emigration. The bullæ themselves are all sub-corneal, some of them, indeed, have their bases covered by a few layers of cornified cells. The *cover of the vesicle* contains, like the peripheral horny layer, well-stained mycelium, mostly in loops. It forms a pattern on the *under side of the cover of the vesicle*, and from here the hyphæ partly project free for a short distance into the inside of the vesicle. They are evidently loosened by the chemotactically attracted serum, and retained on the cover of the vesicle. Only where horny cells still cover the base of the vesicle do we find underneath, a little mycelium. The base of the vesicle formed from the prickle layer, which is swollen, as a whole, and proliferating slightly in its germinal layer, shows no leucocytes. The epithelial cells, which directly margin the vesicle, are in certain places very much swollen and stain faintly, but they still possess well-stained nuclei. A few of these swollen epithelial cells lie loose at the bottom of the blister, but cellular degeneration and the formation of elementary vesicles is never seen.

Towards the middle the horny layer is here and there elevated to form a fibrinous and even a fibrino-purulent vesicle. Those which contain coagulated contents do not present any mycelium in their covering, which probably indicates, that the presence of mycelium hinders coagulation. But in those which also contain leucocytes at their base, we find, without exception, one or more dead pieces of mycelium, swimming free in the blister, and directly surrounded by leucocytes. Mycelium, which dies in the vesicles, consequently appears to attract leucocytes.

Further in begins the crust, which consists in its upper part of

coagulated fibrin, held together by a few thin horny layers. Then come parts densely beset with leucocytes. All the horny layers margining this exudation, contain distorted and stunted but still stained fragments of mycelium. In the centre under the crust there are found, in a few sections, hair follicles, in which the growth of the Trichophyton still proceeds actively. Where these follicles open under the crust, the hypertrophic swollen prickle layer shows, in many places, vesicles filled with leucocytes, small sub-corneal epidermic abscesses pressing the prickle layer outwards, *hyalogenic impetigines*, which are in direct contact with the lower purulent part of the crust. And in the middle of these vesicles, filled with leucocytes and mast cells, (!) there are regularly found, dying, still stainable but distorted and shrunk remains of hyphæ. Those hyphæ which have penetrated into the follicle, here and there break down into oïdia. The surroundings of these central follicles are packed with plasma cells, deep down into the cutis.

Therefore, in contrast to the clinical appearances, which show acute inflammation with hyperæmia and vesicles, only at the periphery, microscopical examination shows, deep under the central crust, living fungi in the once more anæmic region, and a considerable plasmoma formation, which is greater than that of the periphery. Consequently this variety of Trichophyton which, in the first case, induced only hyperæmia and scales, induces on another soil sub-corneal compression vesicles, originally of a pure serous nature, which endeavour to eliminate the fungus. When they have succeeded in that, the exudation coagulates and becomes, under the influence of the dying fungus, purulent, though only to a moderate degree. Further, even in the depths of the skin, leucocytes penetrate into a few hair follicles—no doubt from the death of some mycelium—and constitute small follicular abscesses *—an interesting contrast to the invariably perifollicular purulent inflammations which are induced by staphylococci in the hair follicles.

The more chronic, drier form of nodular Trichophytosis is represented by a case, "Kolster," in which the variety of fungus could not be definitely decided. Here there was found, in addition to the familiar symptoms of a diffuse plasmoma, and great dilatation of the blood and lymph vessels, a *very excessive proliferation of epithelium*, chiefly proceeding from the follicles. This had led, here and there, to complicated, a-typical epithelial growths, similar to those in lupus. In several of the almost unrecognisable follicles there were found, in place of the hairs, one large or several small abscesses, in which only very sparing remains of hyphæ were to be seen.

* In this relation the Trichophyton oïdiophoron rather resembles the acne bacillus, and this analogy makes it probable, that even the latter, in its last moments, has a weak chemotactic action on leucocytes.

This case leads us on to a case of so-called "Kerion" of the head,* which affection is nothing but the nodular form of trichophytosis, on the hairy scalp. The histological appearances are, in the main, exactly the same as in the second stage of the first case; a diffuse plasmoma consisting of typical, equally large plasma cells, which especially occupy the middle and under parts of the scalp, while the papillary body is excessively œdematous. Differences in the appearance are only related to the closely-set hairs of the scalp. By the proliferation of the follicular epithelium, the connective tissue new growth is much separated and pressed asunder in the most varied directions. Since almost all the hairs are invaded by fungi, in hypho- and oidio-form, and many of them are constantly perishing, suppuration is prominent. But here also it is mainly intra-follicular; the abscesses are found in place of the thrown-off hairs, or inside the numerous, irregularly arranged epithelial outgrowths of the follicle. The plasmoma, also, is saturated by pus, at different places, especially at the base of the follicle, so that the process here has culminated in a common abscess formation, an occurrence which is only usual in long-standing cases, or those which are artificially softened by treatment. The surface epithelium also is, in this kerion, much increased, and is covered by a fibrinous and fibrino-purulent crust, which no longer shows any definite remains of trichophyton, but swarms with a variety of bacillus.

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Favus.

Like trichophytosis, favus is a collective name for a whole series of fungus diseases. Until very recently it was supposed to be a uniform disease, for the clinical symptoms were not sufficient to distinguish it. The pure cultivation of the species of favus—we already know nine—first enabled us to distinguish them, and there is commencing a new period in the study of favus, in which we are beginning anew to analyse and control clinical appearances, by the aid of artificial inoculation with pure cultures.

Clinical observation has, as yet, only made us familiar with two different forms of favus, the scaling (so-called herpetic) and the scutular favus, and we assumed that both were produced by the same fungus. This assumption is so far confirmed, for all the known species of favus, so far as they have been inocu-

* For this specimen I thank Professor Tommasoli.

lated, can cause, in addition to scutula proper, simple scaly erythema, the same with vesicle formation, and finally more severe inflammation leading to the formation of crusts. In order to establish a firm limitation of the definition of favus in the future, it is absolutely necessary, in view of the multiformity of the pathological appearances, to endeavour to produce, from every favus fungus, scutula on the human (or at least animal) skin, and on the other hand one will only be able to recognise, as favus, scaling and vesicular erythemata, containing fungi, like favus, when their development into scutula can be proved. The scutulum up to now has been the most important clinical symptom of the unity of favus, and it will therefore offend no one if we retain it, in future, as a combining factor of the different favus diseases. By the formation of scutula the group of favi is distinguished from the group of trichophyta, with which they otherwise share the preference of the fungus for growing into the hair follicles. From many trichophyta the favus group is further distinguished by the fact, that favus never leads to nodule formation in the cutis. On the contrary there is always found, if it last long, a depression of the skin, a considerable atrophy. As general characters of favus, as opposed to other hyphomycetic diseases, we can establish the following points :—

1. They lead to the formation of peculiar fungus cups, the scutula ; 2. They induce, under certain circumstances, a scaly superficial catarrh of the skin with vesicles and crusts ; 3. They always lead, by growing into the hair follicles, to destruction of the hairs ; and 4. They induce, by their long existence, a scar-like atrophy of the skin.

In view of the great significance of the scutula in the diagnosis of favus, the distinction of the scutulum in the histological sense, especially as opposed to less significant products of disease, is of importance. The scutulum is a body of fungus consisting solely of hyphæ and spores, and seated in the horny layer. What distinguishes it from all other fungus growths, inside the horny layer, is the circumstance, that the *threads grow perpendicularly*. Thus it resembles, to a certain extent, the masses of a culture, which are growing on the surface of a firm nutrient medium, and is distinguished from such a mass, formed of ærial hyphæ, only by the fact that, during its development, it is covered by the superficial horny layer and presses it out like a knob. . We may regard it as a globular culture, rounded back on itself, but a-symmetrically formed. For, while the hyphæ, rooted on the basal horny layer, the base of the scutulum, ascend vertically and are luxuriantly nourished, those threads, growing laterally from the horny walls of the scutulum, are shorter, and those on the upper horny covering, directed perpendicularly upwards, are dwarfed or even altogether absent. While the scutulum developes from a tiny, just visible, symmetrical point, to a structure the size of a mustard seed, a pea or a lentil, it is chiefly only the basal and lateral parts which grow; the surface grows very little. Therefore, from the rounded body, there developes one, flattened on its upper side, and by continued growth the lateral parts are pushed up like

walls, and the covering seems to sink in like a dimple. Mibelli also ascribes the dimpled depression of the scutulum to the insufficient nutrition of the mycelium on the surface of the scutulum. Thus is developed the characteristic bowl or cup form, which persists, so long as the mass of fungus is held together by the horny layer, and only in very old scutula, whose horny coverings have given way, is replaced by an almost flat plate.

The scutulum may therefore be regarded as a horizontally extended mass of vertical fungus threads, which is compelled to take the cup form by its enclosure on all sides with horny layer and the bending of its borders. The shape is the same if the scutulum, as is frequently the case, developes from a hair follicle and is then penetrated centrally by one or more hairs. But this method of origin is by no means necessary for the production of the cup form. The frequent occurrence of scutula, penetrated by hairs in the centre, is simply explained by the fact, that inoculation is most easy in the follicles.

The outer (usually the under) zone of the scutulum, consists of rows of hyphæ, closely arranged, growing upwards, without any epithelial structures between them.* The masses, staining with difficulty, which are often found between the hyphæ, consist of dead, empty mycelial tubes. Although this fungus mass forms an independent structure, sharply defined from the horny surroundings, it by no means lies loose in it. It is rather rooted in it by many small threads, and according to their number, which varies in different varieties of favus, the scutulum is more or less firmly adherent to its base.

The inner (usually upper) zone of the scutulum consists of oidio-formed spores, which, in the older cups, run together to a dense central layer of spores. The fungus mass contains neither cocci nor other foreign bodies, epithelial elements or products of inflammation. It is always met as a body, independent of the structures around it. A sero-fibrinous inflammation of the underlying epithelium, by which it is transformed into a crust, elevates the scutulum as a whole. Indeed, by the lateral ingrowing of a neighbouring scutulum, such a crust may again be raised up, and thus one scutulum lies over the other. By the removal of the dividing horny masses, neighbouring scutula may gradually run together.

As is seen, the scutulum is not the simple result of external action on the intra-corneal fungus growth, although such undeniably exists. The specific element which alone is characteristic of this formation, is

* It is often incorrectly stated that epithelium and leucocytes are found at the base of the normal scutulum. Both Mibelli and I found in the scutulum nothing but fungus and a little fluid.

rather quite independent of external influences; it is the tendency of the hyphæ to grow perpendicularly from their substratum, and it is this peculiarity, in the main, which characterises the favus tribe. By its absence, not only are the trichophyta and all other mould fungi separable from favus, but also the less important pathological processes of favoid inflammation from the cups proper.

The slightest, most superficial affection, caused by favus, consists in inflammatory hyperæmia, with swelling and parakeratosis of the prickle layer, and formation of scales, in which the thick, knobbed hyphæ, breaking down into irregular fragments, but without any proper separation of spores, extend horizontally between the horny cells. These *favus scales* have usually only a very short existence; they develope almost exclusively in abortive spontaneous or artificial inoculations.

In other cases the fungus takes a firm root and multiplies vigorously, but without forming the resistant scutulum, and produces a considerable sero-fibrinous inflammation, with œdema of the papillary body, severe œdematous swelling of the prickle layer and the formation of small sub-corneal vesicles, filled with serum and a moderate number of leucocytes. Usually the further growth of the hyphæ is arrested by the influence of the inflammation; they are enclosed in the crusted epidermic layers, and are found in irregular, mainly horizontal extension, surrounded by leucocytes and fibrin, most of them being dead and not staining.* One misses also the regular separation of oidia; instead of them there are large, bud-like processes in the course of the hyphæ, which are no doubt to be regarded as signs of disease in the fungus. By the different direction of the growth, and the close mingling of fungus threads with products of inflammation and horny cells, these *favus crusts* are distinguished from those *abortive and degenerated scutula*, which are observed more often after artificial inoculation than spontaneously.

In this, as in the fully developed scutulum, the fungus forms a flat or spherically formed body in the horny layer. But in place of the regular arrangement of the fungus threads, one sees a tangled mass of fungus, very much bent, and marked with irregular swellings, badly stained, and mostly dying, with, here and there, deeply-stained coarser clumps, somewhat recalling the gemmæ in cultures. There is

* I must not omit to note that many authors regard leuco-serous inflammation as a constant accompaniment of favus. Mibelli has recognised a constant, though varying, recurring exudative inflammation. According to my numerous experiments on animals, the scutular growth, so long as it is undisturbed, is unaccompanied by leucocytic inflammation. This only accompanies the period of invasion of the favus, leading to favus scales and crusts, and again appears in the last stages of the scutulum, when the fungus is dead and foreign organisms grow in the scutulum.

no separation into oidia. Instead of that, one finds in these degenerate scutula, what is possibly the cause of the degeneration, occasional collections of cocci, which are never found in the normal scutula.

The period of favus scales and favus crusts, that is, that of the initial superficial favus catarrh, with horizontal extension of the hyphæ in the horny layer of the surface epithelium, is but little characteristic of favus. It certainly tends in most cases to be accompanied by greater hyperæmia than the corresponding period of superficial invasion in trichophytosis, and the favus spots do not extend so rapidly superficially, and are less easily and quickly communicated than those of the latter. Fundamental differences these are certainly not, for in the different species of both tribes very great differences are found in this connection. It would therefore be very desirable, if we possessed in the microscopical examination of the scales and crusts any certain standpoint for the differential diagnosis. The common view, that one is able at once to make a diagnosis from the fungus threads, is, unfortunately, not tenable. We have indeed always known that the threads of favus are, in general, distinguished from those of trichophyton by their greater thickness and irregularly formed, short joints, and by their more right- than acute-angled division, in short, by a more gnarled aspect. But in certain cases this does not help us. The Favus griseus, for example, frequently shows such slender, long, septate, acutely branching threads, that, without the knowledge of its origin, the distinction would be very difficult.

There is another histological distinction in the relation of the fungus threads to the hairs contained in the scales and crusts. It is indeed a remarkable difference, that the favus fungus, even when growing all through the hair, does not burst it and split it up like the trichophyton fungus. One sometimes finds hairs, permeated by the achorion, far above the level of the skin, and not showing any tendency to splitting and breaking off. The favus fungus has a sort of glueing action on the horny substance, which may be due to the greater development of the fungus membrane in favus, which on the death of the threads remains as a soft, unstained, coherent mass. But, on one hand, this histological distinction is only of value in long-standing cases of both diseases, and, on the other, we have recently discovered a variety of trichophyton, in which the rapid splitting-up and breaking-off of the hairs is absent. So in all doubtful cases of superficial diseases we must still resort to cultivation, to establish a definite diagnosis between Favus and Trichophytosis.

This first acute period of the favus catarrh, after one to two weeks, spontaneously heals, or is succeeded by the *scutular period;* chronic favus proper. At this stage there is not the smallest doubt of the

nature of the disease. While a great number of superficial hyphæ is thrown off with the scales and crusts, and the first inflammatory eruption has subsided, the favus fungus has located itself in certain places, especially in the hair follicle necks, and deposited in the horny layer, rounded bodies of fungus, by means of a new centripetal, no longer centrifugal principle of growth. These still rounded scutula, which here and there shine through the horny layer as small yellow points have no such intense leucocytic inflammatory action on the skin as the free growing hyphæ, for their proliferating ends all turn back from the skin towards the middle point of the mass. This new, specific, favoid principle of growth guarantees to the fungus, on the one hand, a more prolonged, undisturbed existence, but, on the other hand, it induces in time, deeper inflammatory changes in the skin than the acute first period. One may distinguish, in this chronic favus, a hyperplastic initial and an atrophic terminal stage.

The initial hyperplasia is first evident, around the scutulum, in a distinct proliferation of the prickle layer underneath it. The papillary body is at first preserved, indeed on the naked skin the ridge-net usually assumes considerable dimensions, and separates the elongated, diminished, here and there œdematous papillæ, as on preparations which I have from the thigh and the back. While at the side of the scutulum the horny and granular layers are thickened, the latter atrophies underneath the increasing scutulum, so that it is difficult to define the margin between the upper, much flattened prickle cells and the horny cells, with their rod-shaped nuclei, in which the favus hyphæ have their roots. The sub-scutular prickle layer is otherwise normal, or may contain a few leucocytes.

Where the scutula attack a hair follicle neck, the epithelial proliferation extends, corresponding to the amount of growth of the hyphæ, in the fissure between the hair and root-sheath to the prickle layer of the hair follicle, though usually only to the upper third of the hair follicle, although the favus hyphæ, if they have penetrated the hair in the follicular opening, almost always grow through the whole hair shaft, down to the neighbourhood of the papilla. As I recognised in 1880, and as Mibelli has recently confirmed, the bulb, as it is seated on the papilla, is always free from fungus. Mibelli truly says that if the bulb appears to contain threads of fungus, the true bulb is torn off and still remains in the follicles.

If one compares sections containing many favus hairs, for example, from the scalp, which show different degrees of affection of the follicle by the fungus, one always finds that those hairs, which show the least invasion, show it only in the under part of the follicle, inside the hair shaft. Next come those hairs, in which in addition the root sheath is

permeated by fungi. The most marked favus affection is finally found only on a few hairs; here the fungus, as a dense, curly net-work, has penetrated, between the prickle layer and the already much affected hair and root sheath, as far as the middle of the hair follicle or even deeper. These threads do not penetrate into the prickle layer of the follicle, but are rooted on the most superficial, probably parakeratotically cornified layer, and really only represent an extension of the scutulum into the upper, much-dilated part of the hair follicle. Certainly this part of the scutulum is not so regularly formed as that of the surface, and it passes without any sharp margin into the centripetally extending threads of the lower part of the hair follicle. Both the horny layer of the follicle neck and, further down, the root sheath, lose, under the influence of the fungus, their cellular structure and run together to a homogeneous faintly staining mass. The hair sheath is thickened by increased growth of fungus, is irregularly distended and less transparent, but it only rarely shows any splitting. It is very striking, especially on sections of favus scalp, how many papillary hairs completely filled by the fungus one finds in relatively little altered follicles. The invasion of favus causes no premature loss of hair and shortening of the follicles; favus and hair may live happily together.

During these mainly hyperplastic changes in the epithelium there is formed in the cutis—as in deep trichophytosis—a plasmomatic new formation. But this is limited, in contrast to the other, to the subpapillary and perifollicular region, and tends to form smaller groups of plasma cells. There is also absent the deep diffuse plasmoma of Trichophytia nodosa, and therefore a corresponding distension of the favus skin. As to the plasma cells, they are typically developed, are large, filled with granular, very deeply staining protoplasm, and frequently contain two, three, or four nuclei, but further hypertrophy of the cells into chorio-plaques and degeneration into giant cells does not occur. The plasmomatic foci frequently surround the vessels of the upper vascular net, then the coil glands. The cutis lying between always shows a great number of very wide vessels of a venous character, and dilated lymph vessels. The spindle cells, especially in the upper half of the cutis, are increased in number and size, but as hyperplastic cells are not so prominent as the plasma cells. Mast cells are not present in abundance; they are of the round form. The collagenous substance, like the elastic, is only rarefied at the seat of the plasmomatic areas. There is never marked leucocytosis. The coil ducts show peculiar changes, their epithelium shares with that of the surface in the proliferation, and the lumen of the duct is closed. At the same time the duct is irregularly twisted, so that the section shows several solid, round segments of it. In other places we find the com-

mencement of a cystic development in the ducts, which, in older favus skin reaches a still greater degree. Many of these ducts are surrounded by a dense plasmoma. It is somewhat remarkable that the coils themselves only show slight changes; the otherwise frequent dilatation of the lumen is not present, even where the duct in its upper part is obliterated or has become cystic.

If the scutulum last long these progressive changes again subside. The constantly increasing fungus bodies die in their outer parts, which are seated directly on the epidermis, and hardly stain at all. To this is no doubt to be ascribed a constant, slight immigration of leucocytes in the prickle layer. But the leucocytes only reach the border of the scutulum; here they break down and only contribute to the now sharper marginal layer. The prickle layer underneath is reduced to a few flat layers, which, on their under side, still present remains of shortened epithelial ridges, especially on the head. On non-hairy parts of the body the better developed ridge system is usually not completely flattened out, but obliquely laid, the long, thin, stretched ridges and the young papillæ becoming more perpendicular from the centre to the periphery.

In the hair follicles the changes are less; only a few of them are constricted on the surface, and have consequently become cystic. This growing together of the neck of the hair follicle probably depends upon the fact that, before their escape, the hairs are bent in many obliquely-lying follicles, and, as I found in one case, gradually wear through the wall of the follicle with the bent part. In these cysts there is found no fat, but a collection of rolled-up hairs, some healthy, some diseased. Like Mibelli I always found an atrophy of the sebaceous glands in the favus follicles. But apart from the formation of cysts there is another symptom. In these cysts there is no fat, because the sebaceous glands of the favus hairs are regularly atrophied, but there is a convolution of bent and rolled up, partly healthy, partly favus hairs. But another symptom also shows that a retention exists at the follicle mouths. Most hair follicles contain an unusual number of hairs. While normally the young hair, after the throwing off of the old hair, grows into the old follicle, in favus the ascent and casting of the old papillary hairs is made more difficult. There is gradually formed around a central hair a series of epithelial processes, which lead to the formation of hairs, and permit the ascent of these into the old upper parts of the follicles. The latter sometimes contain as many as four to six papillary hairs of the same calibre, of which only a few, the older ones, are affected by favus. While usually, in chronic inflammatory diseases of the scalp, we very soon find a general throwing off of the papillary hairs, with shortening of the hair follicles, a

new formation of young hairs from the bed hairs, and therefore an unusual multiformity of the conditions of the hair, this is absent in long-standing favus, so long as the scutula are undisturbed. After treatment and cure of the favus, this form of retention of the papillary hairs ceases.

Numerous and manifold are the cysts of the sweat gland canals. These are found only in the duct, but in its whole length, especially at the commencement inside the loose connective tissue which surrounds the coil, and then again, after penetrating the firmer layers of the cutis, in relation to the upper vascular net, shortly before its opening into a hair follicle or on the surface. While the latter distensions are almost always purely globular, the lower cysts are mostly pear-shaped, with the thicker end downwards; more rare is a simple cylindrical dilatation of the whole duct or certain sections of it, or spiral dilatation of the upper or under end. The walls of these sweat cysts consist of three or four layers of smooth, very equally thinned and widened epithelial cells, with rod-shaped, flattened nuclei and clear glistening protoplasm. The inner layer of cells presents no cuticular border. Thicker sections show, in these cysts, a fine granular, greyish-yellow, coagulated-looking substance, concentrically contracted from the walls, which, on the finer sections, has usually fallen out. The coil glands on these preparations are scarcely changed, in particular they have not undergone cystic degeneration.

The cellular infiltration of the cutis still consists chiefly of large plasma cells, but it is very much loosened, and contains a number of large lymph spaces. Especially can a retrogression of the plasmoma be recognised in long-standing cases of favus of the scalp, where no collagenous tissue is again formed. Consequently the cutis becomes excessively thinned, the hair follicles are obliquely laid, and the coil glands approach very near the surface. But the disappearance of the cellular infiltration and the atrophy of the cutis is by no means so distinct on the non-hairy parts of the body as on the scalp. This may depend on the great resistance which the pressure of the scutulum experiences from the skull.

This plasmoma formation, with resultant atrophy of the cutis, shows a great analogy to the conditions in Ulerythema, especially Ulerythema sycosiforme. But they cannot be identified with these. For the cellular infiltration in Ulerythema is distinguished by the fact that, from the commencement, it is permeated by wide lymph spaces, and under all conditions leaves a rarefied cutis behind it. The favus plasmoma is, on the contrary, denser, and, after it has healed, collagenous tissue takes its place, if external factors, such as the pressure of the scutulum on the skull, do not hinder it. The atrophy of Ulery-

thema cannot be avoided, it follows both spontaneous and artificial healing; in order to prevent the formation of the favus atrophy one has only to remove the scutula sufficiently early before they have produced a pressure atrophy of the infiltrated cutis.

The elastic tissue is, I agree with Mibelli, in the second atrophic stage of favus, completely atrophied. Circumscribed suppuration and hair follicle abscesses, as in excessive trichophytosis, are not present at this stage.

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Folliculitis scrophulosorum (Lichen scrophulosorum Hebra-Kaposi, Acne cachecticorum Kaposi).

This disease consists of brownish red papules, the size of mustard seeds, mostly localised at the mouths of the follicles, covered with fine scales, which appear especially on the abdomen and back of those children and young adults, who are evidently scrophulous (showing swelling of the glands, scrophuloderma and disease of the bones), and after lasting for months or years, disappear. Some nodules may show pustules at their apices, others livid and even hæmorrhagic halos, especially on the legs (Lichen lividus, Acne cachecticorum). The use of the word lichen for this affection should properly be universally abandoned. The views on this peculiarly limited and certainly not pure tuberculous affection balance between two opposite points; either it is a rare manifestation of tuberculosis of the skin (H. Hebra, Sack, Jacobi) or a peculiar form of folliculitis, which only developes on cachectic or tubercular skin (Besnier). If the former view is correct, we can still not regard it as a simple tuberculosis of the skin, but as a dermatosis, which—according to Kaposi's view—may even be manifested in seborrhœic eczema in the scrotal and pubic regions, and only arouses the latent perifollicular tuberculosis, and one would have to regard it as a mixed infection (Tuberculosis and some other dermatosis). The latter view appears to me to be clinically the more correct, for every true tuberculosis of the skin tends to develope into Lupus or Scrophuloderma, and not to heal spontaneously. According to this view this peculiar folliculitis would add itself to other primary tubercular affections, as pityriasis versicolor does in the last stage. On this ground I have placed it among the folliculitides and not with tuberculosis.

The first histological investigation of this disease was by Kaposi, who found a perifollicular inflammation, characterised by cellular infiltration and exudation. This is limited to the immediate neighbourhood of the follicles and the sebaceous glands, and the perifollicular

papillæ. Masses of horny layer, sometimes soaked with pus, occupy the mouths of the follicles, and represent the scale on the top of the spot.

Recently and simultaneously Sack and Jacobi have discovered new histological facts, which appear to give the affection a more specific tubercular stamp. They both found, in the connective tissue of the nodule, the structure of miliary tubercle—namely, collections of "round cells," "epitheloid cells," and giant cells. Further, Jacobi succeeded in once distinctly recognising a rod, stained like a tubercle bacillus (Gabbet's method), while Sack sought in vain for typical bacilli. Inoculation on guinea-pigs was, in Jacobi's hands, negative. He lays no special value on the tubercular structure of the nodule, but believes, in view of that and the acid resisting bacillus, together with the clinical conditions, that the diagnosis of perifollicular tuberculosis is demanded.

Sack more thoroughly describes the histological details. One of the nodules which he examined did not correspond to a follicle. The prickle layer here was degenerated, showed dropsical and granular degeneration, and was covered by a thick scale, depressed in the centre. Underneath the degenerated epidermis, the cutis was transformed into a caseous area, which contained in a reticulum half-a-dozen very large, typical giant cells, with hundreds of nuclei. The periphery of the nodule consisted mainly of leucocytes and plasma cells. In the perifollicular foci, on the contrary, the giant cells were more evenly distributed around the follicle, and the small-celled infiltration was more pronounced. The infiltration zone was always sharply margined from the surrounding, simply hyperæmic skin.

From these observations Sack believed that he could definitely decide the tubercular nature of the affection. And indeed the caseation of a tubercular-looking granuloma—syphilis being excluded—is very much in favour of tuberculosis. But in the discovery of plasma and giant cells, the reader of the previous sections—especially that on folliculitis—will no longer recognise a proof of tuberculosis. An absolutely defined distinction can only be made by the recognition of virulent tubercle bacilli in the nodules, or by the recognition of some organism which invades the hair follicle, and from there induces the perifollicular inflammation. Clinically I regard the latter as the more probable. At least our present knowledge is not sufficient completely to explain the nature of the nodules.

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Perifollieulitis suppurativa conglomerata Leloir.

Under the name, Périfolliculites suppurées et conglomérées en placards, Leloir has described an affection, clinically well-defined, which is frequently observed in Paris, more rarely elsewhere. It consists of sharply-defined, livid red, round, not polycyclical, soft patches the size of a sixpence to half-a-crown, which are elevated perpendicularly from the healthy surroundings, and show an uneven surface covered with pus and crusts. After they are removed, it is seen to be pierced like a watering-can, corresponding to the mouths of the follicles. The patches, usually single, rarely in collections, are generally on the fore-arm and the backs of the hands. They run a sub-acute course, reaching their height in eight days, and remaining in this condition usually for several weeks. There is no general disturbance, and the lymphatic glands do not swell.

From the histological examination Leloir believed that he could especially exclude trichophytosis; he never found mycelium in the lanugo hairs. The prickle layer between the follicular cells and the horny layer is partly thinned, partly thickened; the former contains a moderate number of leucocytes, and frequently the commencement of vesicle formation; the latter is parakeratotically altered. The hair follicles are filled with thrown-off horny layer and pus cells, and are often cystic; the prickle layer of the hair follicles, therefore, shares in the catarrh of the surface epithelium, as do later the sebaceous glands of the lanugo follicles, and thus the follicular cysts are greatly developed in breadth and depth, and opening on the surface produce the watering-can appearance. These widely-dilated follicular cysts become clothed by a frequently thickened prickle layer, which now and again carries ridges, through which the pus of the surroundings gets into the cysts. Sometimes they are completely eliminated by the perifollicular suppuration.

The perifollicular inflammation varies in extent and form. In some cases the papillæ are very much swollen and œdematous, and some of them run together, thus giving to the surface a papillomatous form (papillomatous variety); in others the lower layer of the cutis and the hypoderm share in the inflammation (phlegmonous variety). The coil glands appear to be only secondarily affected in the inflammatory process. The foci of inflammatory cellular infiltration contain giant cells, especially in the central regions of the skin.

As to the probable cause of the affection, Leloir found in the lymph spaces of the cutis, in two cases, cocci, sometimes singly, sometimes embedded in masses of mucus, and in these cases he also cultivated them from the blood of the patients. In view of the great resemblance which this affection has, both clinically and histologically,

to certain forms of kerion in trichophytosis, it will be important, in future investigations, to lay special value on the definite exclusion of a trichophytic infection of the lanugo hair follicles. I have seen one case of kerion of the head of a child, which appeared in isolated patches, and so closely resembled Leloir's drawing (Table 5, figure 1), that I felt almost compelled to diagnose it as this condition, especially as in the crusts and hair only cocci and no mycelium were found. But the excision of a piece of skin supplied preparations, in which the fungus was recognisable, *only at the base of the unsuppurated follicles.* There are then cases of trichophytosis, in which the fungus rapidly perishes at the surface, in the upper part of the follicles, and in the affected and cast hairs, and which give rise to profuse suppuration and deep inflammation of the cutis, in the form of marginate patches. In this advice to be cautious, I of course do not mean in any way to doubt the character of Leloir's affection, as a special disease, independent of trichophytosis.

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Folliculitis exulcerans (Lukasiewicz).

In an otherwise healthy female patient there appeared nodules, the size of a pin-head to that of a small pea, which, by peripheral extension of the infiltration and the elevation of the borders into new nodules, formed patches of infiltration of different size. They were especially localised on the extremities, broke down into ulcers, and had a clinical course, uninfluenced by any application. Some nodules slowly healed spontaneously, but most of them had to be removed surgically after twenty-three months' stay in hospital. During this period, periosteal swellings appeared, but later spontaneously disappeared. There was no swelling of the lymph glands ; tuberculosis, syphilis, and diabetes were excluded.

Lukasiewicz found, in the smallest nodules, a thickening of the prickle layer and an enlargement of the papillæ, with moderate perivascular cellular infiltration, which extended along the vessels into the deeper parts. Here, even in this early stage, there were found, around the hair follicles, sebaceous and sweat glands, sharply defined, irregular collections of cells, which consisted outside of round cells and inside of epitheloid cells, with a few large giant cells with marginal nuclei. The glands themselves were still intact ; the subcutaneous tissue during the whole process remained normal.

In the older nodules the epidermis is permeated by "round cells" (leucocytes ?), the horny layer is thinned and almost ruptured. The

sub-epithelial infiltration increases in degree, and now consists of "round cells" and "epitheloid cells." In the sub-papillary stratum there are found foci containing giant cells, and single giant cells. The sweat glands occasionally pass into this new formed granulation tissue, while the peripheral loops of the glands are still recognisable. Even in these perispiral foci, there are found, in addition to a few "round" and "epitheloid" cells, many giant cells with marginal and central nuclei.

More advanced nodes show a confluence of the previously isolated foci into a connected cellular infiltration, which reaches from the stratum sub-papillare to the coil glands. The epidermis is here and there thickened over them, at other parts it is thinned and finally disappears. The surface of the ulcer shows, at first, many giant cells, but their number gradually diminishes. The base of the ulcer consists almost entirely of round cells, later of spindle cells, and thus the scarring begins.

Lukasiewicz concludes from these observations that the affection has most resemblance to the granulomata, and of these, to tuberculosis. The latter is to be excluded, partly on account of the absence of tubercle bacilli, partly by the want of virulence of excised pieces, which, inoculated under the skin of the abdomen, and into the abdominal cavity of guinea-pigs, produced no tuberculosis.

Pollitzer believes, in view of the mainly perispiral localisation of the infiltration at the commencement, that it is a variety of inflammation of the coil glands, analogous to that described by him.

The very important different clinical appearances of the case of Lukasiewicz on the one hand, and the cases of Spiradenitis suppurativa on the other, make such a conclusion premature. Both affections must be much better studied before this conclusion is drawn. In other cases of Folliculitis exulcerans, special attention must be paid to the origin of the inflammation, and to the relation of the central follicle, before coming to a decision, whether the follicle or the coil is affected, and which is affected first. The presence of giant cells, "epitheloid" and "round" cells in areate arrangement, by no means makes it necessary to remove an affection from the deep epidermic inflammations (folliculitis) to the inflammations of the cutis, as the description of the previous affections (acne, trichophytosis, etc.) has sufficiently proved. In this arrangement I have retained Kaposi's diagnosis: Folliculitis, which Lukasiewicz believes he has proved. For the actual decision of this, a more thorough examination of the follicle is necessary than he has given.

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(b). *Inflammations of the coil glands.*

Spiradenitis disseminata suppurativa.

(Acnitis Barthélemy, Hydradenitis destruens suppurativa Pollitzer, Hydrosadenitis disseminata suppurativa Dubreuilh).

An eruption, lasting from one to many years, of pale, movable nodules, of the size of groats, lying deep in the cutis or subcutaneously, which, growing to the size of peas, become immovable, then red, covered with a vesicle and central crust, and, after long existence, either dry up and throw off the crust, or suppurate, and then heal with a deep retracted scar. The nodules are seated preferentially on the hairy scalp, the face, maxillary regions, ears, neck, extensor surfaces of the extremities, elbows, knees, buttocks, ankles, backs of hands and feet, palms and soles, but they leave the flexures of the elbows and knees, the abdomen, the genitals, and the upper and central parts of the back, relatively or altogether free. They cause no pain and are not penetrated in the centre by a hair. There is no general disturbance.

With Dubreuilh I regard the cases, described by Bronson and Pick, as universal forms of Acne varioliformis, as cases of this condition, as well as the Acnitis of Barthélemy, and further also Giovannini's acute case of "Hydrosadenitis."

The histology of this recently described affection has been pretty well explained by the careful works of Fordyce, Pollitzer and Dubreuilh. In the centre of the nodules these authors found a coil gland, often a group of them, between whose loops a cellular infiltration had collected. With the enlargement of the nodule these perispiral masses of cells run together to a collection of cells, at first enclosing the individual coil and its adjacent fat lobule, later uniting into a more conical or flat, dense cellular infiltration, which occupies the under layer of the cutis, and from here sends processes towards the surface, sheathing the coil ducts. The epithelium of the coils shows changes, the cells swell up, separate, loose their sharp contour and the deep stain of their nuclei, and finally run together to an irregular homogeneous mass, beset with pale nuclei, which is for a time separated from the cellular infiltration outside, by the well-preserved musculo-elastic membrane. Then this also disappears, and the loops of the coil can only be recognised with difficulty, in the middle of the cellular infiltration, by the size and pallor of their nuclei. These degenerated epithelial cells sometimes form giant cell-like clumps, and Pollitzer recognises in them the origin of the numerous giant cells, which, according to all authors, are present, while Dubreuilh regards them as simply *like* giant cells, since he has seen ordinary non-epitheliogenic giant cells—on sections shown him by Darier. On the other hand Dubreuilh agrees with Pollitzer, that the epitheloid

cells of the infiltration are developed from the degenerated epithelium, while the other authors (Giovannini, Barthélemy, Darier, and Jacquet) derive the epitheloid cells, as usual, from the connective tissue cells, outside the coil glands.

It is a fact, and in this all authors are agreed, that in the cell masses, which distinguish the affection, in addition to very many, mostly peripherally arranged leucocytes, so-called epitheloid and giant cells are present. Then they all agree that the degenerated epithelium of the coils is, in the later stages, very difficult to distinguish from the surrounding cell masses. But, in view of the previous want of a good protoplasm stain, the nature of the small-celled, perispiral infiltration is still questionable, as the indefinite expressions "indifferent," "embryonic," and "round" cells indicate, and we do not know how many of them are connective tissue cells, and how many leucocytes. Equally uncertain is the question whether the degenerated epithelium represents the larger cells of the infiltration (so-called "epitheloid" and giant cells), whether the giant cells all proceed from the coils, as Pollitzer has it, or whether one has to distinguish both connective tissue giant cells and epithelial giant cell-like structures, as in lupus of the palm of the hand (which see).

Through the kindness of Dr Dubreuilh, I obtained a fresh papule, preserved in alcohol, from one of his cases, and can therefore contribute a little in answer to this question; while, on the other hand, certain of my observations tend to throw a new light on the pathogenesis of the affection.

So far I can only confirm the statements of the writers, that the process is an inflammation in the depth of the skin as far as the coil glands, which, from a greatly infiltrated centre, spreads in different directions. I also agree with Pollitzer and Dubreuilh, that the coil epithelium primarily shows certain changes, which represent, not the results of the cellular infiltration of the surroundings, but its cause, for they frequently precede it. The establishment of the process, as a special form of inflammation of the coil glands (spiradenitis), is therefore justified. Peripheral glands show the slighter initial changes, the central ones the graver, later ones.

The order of the changes is something like this. At first the whole coil swells up, partly from enlargement of the epithelium, and partly from dilatation of the lumen, which latter sometimes gapes widely. Whether an increase of the cells in the coil takes place, I cannot decide, for I found no mitosis, but I do not think it probable. Very soon the perispiral connective tissue cells commence to multiply, in the form of new and pretty large spindle cells and of plasma cells.

The latter are of different sizes, and are irregularly distributed; sometimes they possess a very large cell body, but most of them have only little granular protoplasm. This perispiral infiltration is constantly becoming denser, the cells are small, but deeply stained, and are easily distinguished from the few leucocytes which, at this stage, are mixed up with them. At the same time there is a regressive change in the coil epithelium, the cell bodies become cloudy and homogeneous, and partly run together. With good methyl blue staining the nuclei take the blue only very faintly, and the protoplasm of the cells only a bluish-green colour like necrotic tissue, and the contents of the coil glands are, therefore, in sharp contrast to the deeply blue, perispiral infiltration, which surrounds the loops, close up to the membrane of the coil. At this stage there is nothing present which could be regarded as epithelial giant cells.

Still more central coils show an advance, in that in the perispiral infiltration a number of different-sized giant cells appear, while some of the connective tissue cells, like those of the coil epithelium, become cloudy and homogeneous, take a greenish stain with methyl blue, and their nuclei only stain faintly. In the coils the regressive metamorphosis is still further advanced. All the protoplasm has run together into irregular, scarcely staining masses, which still contain the faintly-stained nuclei of the original epithelium. Part of this cellular debris is absorbed, the loops collapse, and thus it is that necro-biotic masses of protoplasm, with groups of faintly-staining nuclei, are found isolated in the perispiral infiltration, showing a certain resemblance to giant cells. But, with a good protoplasm stain, the very great differences between real, living, deeply-staining, growing, connective tissue giant cells in the neighbourhood of the coil, and the necrotic, scarcely stained remains of coil epithelium, is as clear as possible. Finally, the latter is absorbed and no longer visible, and only the perispiral infiltration is evident, in place of the necrotic coil.

This regressive metamorphosis of the coil often affects only parts of a gland, especially the distal, so that one may study the successive changes in one single gland.

According to my investigations, we have therefore to do with an inflammatory swelling of the coil epithelium, with resultant necrobiosis, whose place is occupied by an infiltration, partly plasmomatic and containing giant cells.

Further, I can confirm Dubreuilh's statement, that the inflammatory infiltration extends outwards, along the coil ducts, up to the surface epithelium, and the statement of all the writers that the cellular infiltration extends along the blood vessels, especially the papillary ones. Indeed, the cellular mantles, sheathing the blood vessels, are often of

considerable breadth, and are pretty sharply marked off from the rest of the cutaneous tissue, in which only the spindle cells show hypertrophy. These perivascular infiltrations contain mostly spindle and small plasma cells, and only a few leucocytes. Here also the irregular distribution and size of the plasma cells is remarkable. Close together, we find many multi-nuclear plasma cells and smaller and larger chorioplaques. True giant cells with acidophilic protoplasm, often of enormous size, are found along the central hair follicle. And here I come to a point in the pathogenesis of the affection, which, if it can be confirmed, is of great importance.

I find the gravest changes in the whole papule, concentrated on one of three hair follicles which are enclosed in the papule, and this occupies the centre of the papule and carries at its apex a pustule, with changes of the surface epithelium around it, such as Dubreuilh describes. The whole hair shaft is softened and surrounded by leucocytes, and the prickle layer of the follicle is necrosed in its inner layer next the hair; the epithelium only takes a faint nuclear stain with methyl blue, and the protoplasm, a greenish tint. In the under part of the follicle the necrotic processes extend still further, so that here part of the follicle wall also becomes necrotic, and the contents of the follicle communicate with the wide lymph spaces of the surrounding cutis. Accompanying these great changes of the follicular epithelium, the connective tissue all round the follicle is infiltrated with cells to a breadth which, in the under part, is much greater than that of the hair follicle. This infiltration consists mainly of spindle cells, with a few scattered plasma cells, and one or two groups of very large giant cells. This perifollicular, infiltrated cutis is distinguished by two symptoms, which give to the infiltration in every section a special character, and are not found in other perifolliculitides. First, the collagenous tissue between the cells is softened, loosened, rarefied, and with good methyl blue orcein stain, no longer takes the reddish orcein colour, but a faint, greyish blue, diffuse stain, in which the individual fibrillary bundles cannot be recognised. This softened and degenerated collagenous substance is then permeated by very roomy lymph spaces, which occupy the place of the vanished collagen. We have, consequently, a simultaneous softening and disappearance of the collagenous substance, quite comparable to the softening of the prickle layer of the hair follicle and the coil epithelium. But it has no resemblance to the resorption (without previous softening and alteration of the staining power) of the collagen in Lupus, or in Ulerythema centrifugum and sycosiforme. In many places the follicular epithelium is elevated *in toto* from the softened and infiltrated perifollicular tissue, in other places there is a limited leucocytosis, which extends into the hair

follicle and into the surface epithelium surrounding the follicle mouth. In the neighbourhood of the follicle one meets many swollen, homogeneous, cloudy, rounded cells, with faintly staining nucleus and protoplasm, which are to be regarded as necro-biotic, and possibly correspond to the "epitheloid" cells of certain authors.

Some of the large giant cells are found in the cutis around the follicle neck, but the largest ones surround the under part of the follicle, and a group of especially large ones corresponds pretty exactly to the neighbourhood of the sebaceous gland, which is not otherwise evident. It seems to have suffered the same fate of softening and necrosis as the coils.

The coil glands surrounding the fundus of the necrotic follicle are the ones most severely affected, so that one must regard them as the parts first affected after the hair follicle. The fat lobules in connection with them have lost their fat, and are converted into infiltrated, softened islands of tissue.

Like the other writers, I was unable to find, in spite of the most careful examination, any kind of micro-organism. No staining method familiar to me showed, either in the coil glands, the central necrotic hair follicle, or in the small pustule lying above it, one single micro-organism. Nevertheless all the changes, the necrosis of the epithelium, the progressive and the regressive changes of the connective tissue, and especially the many and large giant cells, point to an infectious inflammation. In my case I regard infection through the hair follicle as the most likely. It is in favour of this, that that is found in the centre of the papule, and that it has mostly undergone necrotic changes and is directly surrounded by those coil glands which have undergone the gravest alterations. A secondary change of the hair follicle from the coil glands, the hair follicle being simply used as a convenient way out for the inflammatory focus, would not go well with the facts, that the hair follicle is found equally affected in its whole circumference, that in the neighbourhood of the follicle neck the severest changes are met (giant cells, softening of the cutis), and that apart from it no other centre of the disease is present. According to our general experience, it is also more probable that the, as yet unknown, infectious germ penetrates in the ordinary way down the hair fissure into the depths of the skin, and from here (like the pyococci) makes its way into the neighbouring tissue. If this should be confirmed by later investigation, the peculiarity of this infection would only lie in the fact that the germ first causes distinct changes in the depths of the hair follicle, and that its products exercise a specific, injurious influence on the surrounding coils, sebaceous glands, and fat lobules. In this sense it is perhaps not unimportant to note, that the sebaceous

glands of the otherwise unaffected hairs show, at their bases, a striking coalescence of the sebaceous cells, and an elevation of the epithelium from the gland membrane, which changes cannot be ascribed to an influence from without, for the upper parts of the same sebaceous glands are completely normal. The redness, the projection, and the crust formation of the nodule, as well as the ultimate suppuration with throwing off of a plug, may be equally well explained by this view. The assistance of ordinary pyococci is no more required here than in Acne pustulosa.

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(ββ). Local infectious Inflammations of the Corium.

The local infectious inflammations of the cutis permit of a definition, according to our chemotactic theory of inflammation, as simple and clear as that of those of the epidermis. In them the inflammatory agent is found in the cutis, instead of in the epidermis. Although in almost all cases the infection enters through the epidermis, the organism first finds its proper soil, its resting place, and first produces its characteristic changes, in the cutis.

That the infectious dermatitides may be so easily divided into two large groups, according to the seat of the cause of the disease (which is both etiological and anatomical) evidently depends on the fact that the organisms may thrive better in one or other layer, and therefore the division of these inflammations into epidermic and cutaneous is not artificial but only natural and necessary.

Thus it is that an organism—such as, for example, the bacillus of soft chancre, when it first attacks the epidermis, causes an inflammation. But this preliminary affection of the epidermis can scarcely be recognised clinically, and the bacillus immediately attacks its proper soil, the cutis, and produces here, in every case, an ulcer proper, which alone is characteristic of the disease. In other cases those micro-organisms, which are only suited for development in the cutis, are merely caught for the time being in the epidermis, as, for example, the Lepra bacillus. But it produces here no specific affection of the epidermis, no infectious inflammation, as it does in the cutis; it leads here only a transient, accidental, saprophytic existence. Indeed, in

most of these organisms, infection is only possible if the organism is at once brought into contact with the cutis, through the epidermis; every doctor knows that vaccination is only successful if the papillary body is slightly wounded.

Important exceptions to this rule are a few organisms, viz., the pyophoric causes of infectious diseases, the Staphylococcus aureus and the Streptococcus of erysipelas. These possess a remarkable adaptability, which fits them for a parasitic existence, both in the epidermis and the cutis, and to this is evidently due the important rôle they play among infectious diseases; to this adaptability they owe their almost ubiquitous presence. It is fortunately not necessary to create for these organisms a half-way house of "infectious inflammations of the whole skin," for the epidermic inflammations on one hand, and the cutaneous inflammations on the other, are so different in their clinical characters, that it was long before we regarded them as a unity, and it was not so much clinical, as etiological investigation, which brought about this advance. Up to the year 1887—that is, to Bockhart's work on Impetigo, Furuncle, and Sycosis—Impetigo only led a somewhat confused existence in dermatological work, and the surgeons treated for furuncle. As the following will show, histological investigations followed step by step on the footsteps of etiological, revealing the transition of impetigo into furuncle, and stamping both with the mark of a uniform infection. And the differences in the histological appearances are seen to be less, and more gradual in their transition, than clinical observation appeared to show. But in spite of this it is possible, and I have succeeded in retaining impetigo and sycosis, histo-pathologically, among the superficial and deep epidermic inflammations, and furuncle among the inflammations of the cutis.

If this view of the etiological unity has been justified, in favour of a pre-existing clinical multiplicity, in the staphylogenic suppuration, it is still more so in the microscopical investigation of the streptogenic affection. For, in comparison with the staphylococcus aureus, the streptococcus is only specially adapted to the cutis, so much so, that it was left for histological investigation to discover and describe the streptogenic pustule of the epidermis.

Among the inflammations of the cutis these two form the first and second group of the sero-fibrinous and the purulent inflammations. Why I do not regard the streptogenic inflammations as typical suppurations will be evident from the description. They rather approach the necrosing inflammations, which form the third group.

In the latter, the position of glanders requires explanation. Glanders may really claim a triple place—first, here in the localised chronic inflammations, then in the neighbourhood of syphilis, among

the generalised chronic inflammations of the cutis, and finally another, near Variola, as a form of acute exanthem. But I had not the necessary material for even a double representation, and, for a thorough histological description of glanders of the human skin, I found in the literature at my disposal practically no help. I have endeavoured to fill up this gap, so far as I could, from a case of acute Glanders which came under my observation, and I have placed it provisionally, as will probably be expected, near Anthrax and Actinomycosis; but much remains to be done in this connection.

The fourth group is that of the so-called granulomata. They form the group of the infectious inflammations of the cutis with a tendency to new growth. From them may be separated those affections which are regionally limited, and which form a natural sub-group. There then remain these general diseases, which have as yet been regarded as granulomata in the narrowest sense, chief among them being Tuberculosis, Syphilis, and Leprosy. They form a step towards the acute exanthems—the general affections with only symptomatic inflammatory skin affection.

(a). *Serofibrinous Inflammation.*

Erysipelas.

The well-known diffuse reddening and swelling of the skin, caused by the presence of streptococci, and everywhere known as "Rose," appears under two very different forms.

The most distinct, and therefore typical form, is distinguished by a sharp border of inflammation, more or less notched, deeply red, and extending serpiginously. This is accompanied by œdema, the formation of vesicles and crusts on the surface, and fever synchronous with the advance. In severe cases it may lead to patches of gangrene.

In addition to this true, acute, *spreading* erysipelas, there is often seen a stationary redness of the skin, also caused by streptococci, in connection with open wounds, tubercular, syphilitic and leprous ulcers, ulcers of the leg, suppurating fistulæ, especially from carious teeth, eczema, folliculitides, and catarrhs of the mucous membranes, especially of the nostrils. In this chronic stationary erysipelas the redness is less, and merges gradually into the healthy surroundings, while the œdema is often as marked as in acute erysipelas, so that the redness may be completely obliterated (white erysipelas). These cases run their course without fever, and are distinguished by their slow, and occasionally regularly remitting character, which leads to the mistaken assumption of true recurrences. They often show their erysipelatous character by passing into the acute febrile form.

We consider here only acute spreading erysipelas, the type of fibrinous inflammation of the cutis, stationary erysipelas we will meet again under the progressive infectious inflammations (see Elephantiasis nostras).

A large amount of investigation has recently been devoted to the

histology of Erysipelas, though not to its dermatological aspect. The well-known work of Koch and Fehleisen originated this, but most of the work done has been almost purely bacteriological. The many different, and apparently contradictory observations led the observers to diametrically opposite views, which are by no means yet reconciled. It is sufficient to draw attention to the two most important points of divergence. The first is connected with the names of Metschnikoff and Baumgarten, of whom the former finds an inverse proportion between the assemblage of leucocytes and the proliferation of cocci in the skin, and regards this as a strife between these two powers. The latter, on the contrary, considers that the leucocytes only appear after the bacteria, and recognises no distinct opposition between them.

The second point of divergence concerns the question, whether a sharp margin can be drawn between pure erysipelas on the one hand and phlegmon on the other, in other words, whether the so-called phlegmonous or pyæmic erysipelas is true erysipelas, or not rather induced by another organism than Fehleisen's coccus (Hajek), or whether important differences exist between erysipelas and phlegmon, between the streptococci erysipelatis and the streptococci pyogenes (v. Eiselsberg, E. Fränkel and others), and whether the two processes, so different clinically, are simply different grades of the same affection.

Both points of divergence are due to the fact that there actually exist in the histological appearances of erysipelas, certain contradictions, which no one who has had the opportunity of examining a large number of cases will deny, and which appear to represent the extreme development of different dermatoses. There are found, on the one hand, appearances with few cocci, in quite circumscribed areas of the cutis, and on the other, those in which the cutis is permeated by innumerable cocci. Moreover, the emigration of leucocytes plays in many cases an important, in others only a subordinate rôle. Both sometimes concur, but not always.

Therefore it is not difficult, with a fixed idea, to find appearances, apparently confirming the theory, either for a monistic or for a dualistic view of the process, and also appearances, which prove both the predominance of the leucocytes and of the streptococci. Thus we must be doubly cautious in the explanation of the appearances, and seek, more than we have previously done, for criteria for the establishment of those symptoms, on which the previous views are founded, such as that of the death of the streptococci, the breaking down of leucocytes, and the intra- or extra-cellular position of the cocci. After we have sketched the different appearances, our conclusions on the previous views of the erysipelas process will be evident.

I have before me preparations of sixteen pieces of erysipelas skin from eleven different cases. All show the disease already at its height, that is, a considerable growth of cocci in the very often excessively congested skin, or the process somewhat beyond this stage, although by no means healed. While it is easy to obtain, from fatal cases of erysipelas, pieces of skin showing the disease at its acme, and at all stages of regression, the opportunity is of course rare of examining the initial stage in the living. This want is partly supplied by the borders of older preparations, and regions in them, in which the already healed process is recurring, and finally by the comparison with the fresh material from erysipelas, artificially induced on the ear of the rabbit, which I owe to the kindness of Dr E. Fränkel. On the first, not yet erythematous stage of invasion of erysipelas, there is almost complete accord among investigators.

In order to arrange these erysipelata in regular order, according to the age and severity of the process, we require factors which are completely independent of the debatable points, viz., the relation of the cocci and leucocytes. These criteria appear to me to be supplied in the influence of the erysipelatous process on the collagen, elastin, and the cells of the connective tissue. These are readily recognised by appropriate differential staining, and show, long after the leucocytes and cocci have disappeared from the tissue, the severity of the bygone erysipelas. These alterations of the connective tissue are particularly visible on comparison of marginal parts, recently invaded by cocci, with new coccal growths in older erysipelas skin—conditions which, without reference to this change, can scarcely be distinguished.

The collagenous substance shows very different conditions of degeneration, according to the severity and duration of the erysipelas, and also according to its finer or coarser original quality, and these may be arranged in two groups, that of softening and that of coagulation.

The simplest form of softening of the collagen consists in a breaking down of the fibrillary bundles into finer threads, and finally into simple fibrillæ. When these have undergone complete colliquation, the lymph spaces dilate at the expense of the firm connecting substance. The latter extends, in teased-out rarefied condition, into newly formed tissue spaces. In long-standing and healing erysipelas, the fibrous bundles again assume a firmer form and smoother contour, and there remain only much dilated lymph spaces and a looser arrangement of the collagenous bundles.

Where the cutis, at the commencement, consists of thicker, more homogeneous rafters of collagen, there are separated from it feather-

formed, honey-combed, globular parts, of rounded, smooth contour, so that when well stained it has a worm-eaten, perforated aspect.

Further, the rafters break down into shorter or longer smooth masses, which are partly in connection with fibres and partly lie loose in the dilated lymph spaces. This "lumpy fragmentation" greatly resembles the breaking down of the striped muscular bundles, in the same erysipelas preparations. If the lesser degrees of this degeneration are recovered from, the bundles retain, for a time, their worm-eaten aspect, and the spaces then appear to be filled with the homogeneous substance; for with basic acid double staining with methyl blue and orange they take on a yellow colour, in the bluish rafters.

Both *varieties of softening, the simple fibrillary splitting and the lumpy fragmentation*, pass, when the inflammation is fully developed, into the same maximal condition of softening. Then the collagenous substance is converted into a formless debris, taking little stain, which, like the last described condition of softening, can only be removed by resorption.

The degeneration of the collagenous tissue, accompanied by coagulation, forms the acme of the erysipelatous process. After the connective tissue has been split into fibrillæ and rarefied in the ordinary way, a tendency to coagulation sets in. At first it is permeated by a simple net of fibrin, but soon the remainder of the collagenous tissue takes on the form and staining capacity of fibrin, and we find the whole region of tissue converted into a narrow-meshed, coagulated area, with leucocytic nuclei in its spaces, which looks remarkably like a diphtheritic membrane.

On using my method of staining fibrin (Polychrom. methyl-blue, decolor. with concentrated Tannin solution) in my pieces of Erysipelas skin, so far as they come from the face, the elacin fibres also stand out very distinctly in the lower half of the cutis, the more as the surrounding collagen is difficult to stain. Whether the marked development of elacin is simply to be ascribed to the so-called senile degeneration (which may occur in young people), or whether the erysipelas is partly responsible, must await decision, with further experience of the influences of erysipelas on the elastic tissue of other parts of the body. (For description of Elacin, *see* Senile Degeneration.)

The behaviour of the elastic substance in erysipelas is much more uniform than that of the collagenous; it simply perishes from colliquation. As usual in acute inflammation, there sets in simultaneously a disappearance of staining capacity, and all the fibres become thinner. At the height of the process nets of elastic fibres are rarely visible, and only on a few, less affected parts of the cutis. In general, one can better measure the severity and extent of the erysipelas process by the

nature of the elastin than by that of the collagen, though certainly only the existence, not always the age of the process. Where, along with the invasion of cocci, the elastic net is still well preserved, the process must be recent and not very severe; but where it has disappeared, the erysipelas may either be at its height or diminishing.

Smooth and striped muscles show the same changes as the collagen. This is clear in erysipelas of the face, for the subcutaneous tissue always presents marked degeneration of the muscles of expression. These are evident as swelling and simple softening, with loss of the stripes and staining power, and then as a breaking up into masses and formation of cavities: both lead finally to the complete destruction of the muscular bundles. These changes advance relatively slowly, so that, even at the height of the erysipelas, many well-preserved remains of muscle are present, from which one may estimate the duration of the erysipelas.

When the different preparations are arranged in series, according to these criteria, the first and chief result is, that—quite independent of the age and severity of the process—there exists everywhere *an important differenee between the cutis and the hypoderm.* Certainly most of my material comes from infants and children, where the panniculus is in general more developed than the cutis; but the fact is just as clear on the skin of adults (five cases), indeed the difference in the affection of the layers is here, if possible, still more sharply developed.

Further, *the simultaneous affection of cutis and hypoderm* is common to all preparations. The subcutaneous tissue is never free from cocci, the cutis often apparently so; but, in the latter case, one sees from some of the forms of degeneration of the supporting tissue already described, that the erysipelas has previously affected the cutis. In the slightest cases one finds, at least, a diminished staining capacity and a loosening of the collagenous tissue, as well as a great diminution of the staining capacity of the elastic tissue, and a loss of the finer elastic fibres, especially in the papillary body. Further, in running over other sections, one will always find a few single small colonies of streptococci in the dilated lymph vessels. With greater degeneration of the cutis, without the presence of cocci, and still existent invasion of the hypoderm, there can be no doubt about the previous affection of the cutis. The parts which specially contain cocci are still better marked off from the healthy by some good stain (*e.g.*, methyl-blue orcein), and we see at a glance that the cocci are seated in the intermediate tissue, between the blood vessels.

These two facts, taken together, supply the third important one, that the *erysipelas proeess heals up more rapidly in the eutis than in the*

subcutaneous tissue, and seldom reaches such a height as there. It has become an article of belief, from the original investigations of Koch and Fehleisen, that in true erysipelas, relatively few streptococci are found, and only in the outer, not yet reddened marginal zone, while they are not to be found in red, soddened skin. This may, *cum grano salis,** be true of the cutis, and of rapidly spreading erysipelas; of the hypoderm I still maintain, that every erysipelas swarms with cocci, both in the marginal and central zones. Indeed most erysipelata contain, in the subcutaneous tissue, such a mass of cocci that they may take their place beside those affections most rich in organisms, such as leprosy.

Evidently, from its more constant and somewhat higher temperature, the subcutaneous tissue provides better conditions of nutrition for the coccus of erysipelas, which is notoriously sensitive in this respect. We know from daily practice that it is comparatively easy to immediately arrest the progress of erysipelas, and cause it to disappear by mechanical and chemical remedies, such as pressure and cold, or ichthyol, resorcin, carbolic acid, etc. Therefore its conditions of existence, at least at the surface of the skin, cannot be very favourable, and thus the common view of the method of extension of erysipelas is completely confirmed.

The streptococci, inoculated through a wound of the skin, grow through the wide lymph vessels of the cutis, and find, in general, with the free anastomosis of the main lymphatic vessels, no other limit to their extension than that of mechanical external pressure by compression of the lymph tracts, or artificial interference with the medium by drugs. After exhausting the skin, they apparently spontaneously disappear from the cutis, and this must surely be due to the fact that, by their growth, they interfere with the medium. At all events there is no leucocytic wall, which hinders their further extension. But even locally, that is behind the advancing zone of infection, there is no typical emigration of white blood corpuscles into the cutis, which can take up and destroy the cocci, but the growth is simply arrested, and the masses of cocci in the lymphatics and dilated lymph spaces no longer stain,— that is, they die or are washed on into deeper lymphatics, not without leaving behind them, here and there, ominous remains, in the form of single rows of cocci, or denser masses in glœa form.

But certainly, although no typical emigration takes place, there are present in the cutis sufficiently serious changes, of which the persistent degenerations, above described, give evidence. I have had special opportunities of studying these on freshly affected pieces of

* I have never failed to find streptococci in the cutis in pieces from the centre of erysipelas.

skin, chiefly from the ear and the nose. We will next consider the disturbances in the circulation.

The veins and all the capillaries are fully dilated and closely packed with red blood corpuscles. The white corpuscles in the veins are only partly arranged along the walls; we find them more often in small groups in the middle of the vessel; they are distinctly more numerous than normal. The capillaries are in parts continuously filled with leucocytes, but here also no regular diapedesis is evident. The cutaneous arteries are partly also dilated and contain, in addition to red and many white corpuscles, a large amount of *coagulated fibrin;* other parts of them are not dilated but are *completely filled with fibrinous thrombi*, enclosing leucocytes. In a few dilated veins there appear, on cross or longitudinal sections, firm thrombi, consisting of white blood corpuscles, and permeated or surrounded by threads of fibrin, which lie free in the lumen, and have evidently come from arteries or dilated capillaries. We have, as a whole, to do with a paralysis, especially of the veins, a slowing of the stream, with adhesion of leucocytes and with a wide-spread intra-vascular separation of fibrin, especially in the arterial system of the cutis.*

It is quite clear that such severe disturbance of circulation cannot be without result on the lymph stream of the skin, and so we see developed the invariable result of more difficult venous escape, dilatation of the collateral lymphatics, *i.e.*, of all the lymph spaces of the skin. This is no œdema of newly formed spaces, as in urticaria and other spastic œdemas, but a general soddening and distension of the cutis, with loosening of the normal firm texture of the fibrillary bundles. We find the lymph vessels, in which the streptococci grow into larger colonies, dilated by lymph, to which an increasing number of leucocytes and gradually also fibrinogenous substance are added. A few of these lymph vessels contain the same firm, white, fibrinous thrombi as the blood vessels, and many of the thrombi are permeated and surrounded by colonies of streptococci. These appearances very naturally look at the first glance as if the streptococci had attracted the leucocytes; but this is not the case. The streptococci have quite another action than the pyophoric staphylococci, which attract a stream of leucocytes everywhere and from all sides to the skin. For the surroundings of these lymph vessels are almost free from wandering cells; the leucocytes have got here *per viam naturalem*, *i.e.*, the few leucocytes which come from the dilated capillaries and veins, and are found in the lymph vessels, escape by the ordinary paths, and in this way mix with the collections of cocci in the lymph vessels, without

* It is very remarkable, that, in spite of this intra-vascular wide-spread coagulation, erysipelas has no tendency to cutaneous hæmorrhage.

their representing a centre of attraction, and the whole skin being saturated with leucocytes, as in furuncle. The simultaneous separation of fibrin naturally aids in packing the leucocytes into firm thrombi. But this does not lead to their destruction, and with double staining they may be very beautifully demonstrated, *in situ*, in the thrombi. Nor do they take up streptococci; while these, on their side, show no signs of degeneration, but, on the contrary, produce, in these very lymph vessels, the most perfect, long chains.

It is, then, quite clear, that the most important distant action of the erysipelas coccus consists in a breaking up of the blood plasma, without the corpuscular element being directly influenced or injured. There is formed an albuminous body which readily coagulates, and this leads to marginal and complete thrombi, even in the arterial system, but chiefly in the lymph vessels, while the venous thrombi show by their central position that they have been carried there. At the same time this constituent of the blood is, by the chemotactic activity of the erysipelas coccus, transferred in quantity into the lymph spaces of the cutis; a proceeding which takes place in every non-purulent inflammation. From this arises the stagnation in the veins, in spite of their being abnormally wide, and also the albuminous coagulative œdema and the general swelling of the skin.

But a simple œdematous distension of the cutis is not all. In some cases the coagulation of the lymph extends from the lymph vessels into the cutis around, and we have a remarkable appearance, great stretches of the cutis being permeated at right angles to the direction of the fibres by a web of coarse and fine threads of fibrin, in whose meshes well-preserved leucocytes are sometimes, but not always, scattered. But where this extensive coagulation is absent, there are always the above described degenerations of colliquation, the splitting and "lumpy fragmentation." Complete debris-like softening is only present in circumscribed areas. But there is regularly, even in the slight degrees of erysipelas, a disappearance of the elastic fibres and of the spindle cells of the cutis. The nuclei of the latter remain long preserved; in the higher degrees of softening of the collagenous substance they also disappear.

The epithelium also suffers greatly, if the erysipelas persist. Even the simple swelling of the whole papillary body loosens its connection with the surface epithelium. If the papillary body has undergone fibrinous degeneration, with disappearance of all its cells and their nuclei, this degeneration also attacks the epithelium. Its nuclei lose their staining power, their protoplasm being washed out and staining less, but with powerful staining one can still recognise the borders of the cells, and here and there the borders of the nucleus.

An independent swelling of the epithelial cells, and formation of vesicles, does not usually take place, but the degenerated and partly necrotic surface epithelium is elevated, as a whole, from the papillary body, with the formation of very extensive, sub-epithelial, flat bullæ. This is the one and only method of development of bullæ in erysipelas. One only rarely finds streptococci in them, but always coagulated fibrin and leucocytes.

It is remarkable that the epithelium of the surface usually suffers much more in this general poisoning of the cutis than that of the deeper structures. The cells of the coil glands only show swelling, rarely fibrinous degeneration of single cells, and the nuclei are always well stained; the cells of the prickle layer of the hair follicle appear quite healthy in the deeper part of the follicle, and only participate in the degeneration of the surface epithelium, in the neighbourhood of the follicle neck. The greater power of resistance of the deeper lying epithelium of the skin is all the more remarkable and difficult to explain, as it is much more directly exposed to the influence of the coccal growth than the surface epithelium. The coil ducts appear quite normal up to their opening into the surface epithelium.

The simple results of serous and sero-fibrinous inflammation as yet described may, in the cutis, especially in its more superficial layers, reach to such a degree, that whole stretches become necrotic, without any transformation of the inflammation into the purulent one having taken place. Beyond doubt the frequent thrombosis of the arteries and the arterial capillaries has a not unimportant share in this tendency to necrosis, and the greater necrosis of the surface epithelium may possibly depend on it, for the arterial capillaries of the surface are more apt to be filled with fibrinous plugs than those of the deeper cutis and subcutaneous tissue.

The typical erysipelatous inflammation of the cutis is therefore simply sero-fibrinous, and may go on to necrosis of the cutis. We cannot speak in this case of a strife between the leucocytes and streptococci, because there is no proper local leucocytosis.

We find quite another appearance in studying *subcutaneous erysipelas*, and although cutaneous and subcutaneous are never present alone, it appears better on this ground to consider them separately. The greater the development of the panniculus, the more are the special peculiarities of erysipelas prominent, therefore especially so in infants. These exist, on the one hand, in the constant and prominent share of the leucocytes, on the other, in the much more extensive distribution of the cocci in the lymph spaces of the connective tissue, and the associated lesser tendency to form long chains.

The fatty tissue has, in its septa, large blood vessels, while the fat

lobules themselves are surrounded by capillaries. The sheath surrounding the larger blood vessels, with its large lymph vessels and spaces, is the main avenue for the streptococci in the hypoderm. Here they are always present in astonishing numbers, and reach into the muscular tissue, or still more deeply. Here also the blood vessels themselves are unaffected. They are surrounded by a dense mantle of cocci, but the cocci do not penetrate further than the outer layers of the adventitia. In these large vessels there is no separation of fibrin, thrombi are absent, and therefore part of that disturbance to circulation, which is so striking in the cutis, does not exist. On the contrary, the fat lobules, with their capillaries, are the seat of wide-spread formation of fibrin, and often every single fat cell is found enclosed in a sort of basket of fibrin.

But, on the other hand, the septa of the fatty tissue are permeated, in fresh cases of erysipelas, by dense masses of leucocytes, and these come into close relation with the cocci. That is no doubt the reason why there are no longer chains formed here; the cocci are scattered singly or in small rows of two or three cocci, on and around the individual leucocytes. This is the only place where, in the human skin, Metschnikoff's question, whether the leucocytes take up and destroy the cocci, can be answered.

Now I have never seen appearances which point to the death of the streptococci in the leucocyte. The excellent iodine method, especially in Weigert's modification, is in this case unfortunately useless. For it demonstrates all cocci equally well; it affects, as the size of the cocci shows, not the contents alone, but also the mantle of the cocci. Since we rightly regard the staining power as a measure of the integrity of the coccus, we must use the much more sensitive methyl blue stain, which enables us to distinguish the contents of the cocci alone. A careful counter-stain with an acid (not basic*) stain (*e.g.*, orcein, acid fuchsin) shows all the cocci well stained, and at the same time the breaking down of the leucocytes around them. Since, as is seen from specially stained preparations, most of the leucocytes, without distinction, break down in the neighbourhood of the cocci, whether they contain cocci or not, their destruction cannot be ascribed to the penetration of the cocci into them (the phagocytosis of Metschnikoff), but only to the distant action of the cocci in general. In this destruction the body of the leucocyte first breaks up into a fine debris of granules, and the cocci are once more free. The nucleus, with a remnant of protoplasm, is longer preserved, but ultimately breaks down into small fragments and no longer stains.

* Basic stains are not admissible, for they either completely stain the dying cocci or fail to produce any reaction.

And so we have from the pus, which was formed in the septa of the fatty tissue, a debris consisting of broken down masses of cells, in which the cocci—if we must have a fight—remain as the victors. In long-standing erysipelas very careful staining is necessary in order to recognise, in the indistinctly contoured, badly stained mass, which sheaths the subcutaneous vessels, what have been leucocytes. From the larger septa, leucocytes and cocci extend along the vessels into the interior of the fat lobules. But here in most cases the fibrinous coagulation predominates; in the meshes of the fibrin net, cocci and well-preserved leucocytes are seen enclosed beside one another. Only where the process goes on to total liquefaction of the subcutaneous tissue do the leucocytes increase at these places, and are surrounded by cocci; these then penetrate into the leucocytes, which immediately break down, and set the cocci once more free, to finally hold the field in the puriform debris. In this destruction of the fatty tissue the fat of the cells is set free, and their protoplasmic remains now and again form large, multinuclear, round cells. Whether these are identical with Metschnikoff's macrophages I have no ambition to decide. I have not found in my preparations any cells which can distinctly lay claim to this title.

Therefore this process, which appears on all my preparations with the same definiteness, cannot be used in support of the phagocytic theory. For here the cocci do not conquer, because the leucocytes do not sufficiently oppose them; in spite of the numbers of leucocytes which surround them, they themselves do not suffer at all in vitality (staining power). I can speak with some certainty on this point, for, with the methyl blue orcein stain, I have found at other places, really weakened and dying, very faintly stained cocci.

This death of the cocci appears equally spread over large areas of tissue, and is quite independent of a local leucocytosis. It may be observed on stained sections, even with a low power, by a simultaneous clouding and fainter protoplasm stain. I shall later have to return to this appearance. But at the height of the process it is found here and there in the subcutaneous tissue. The lines of pus become converted into cloudy masses, in which single scattered cocci, very small and very faintly stained, are discovered by staining. The "victors," in order to remain on the field of battle, die among the corpses of their victims. I have only rarely met such places in the subcutaneous tissue, but I think I may assume that, in the cure of erysipelas, this represents the normal condition (my material comes mostly from unrecovered or fatal cases). For I know no other possibility of the healing of subcutaneous erysipelas, except through the death of the cocci in the midst of their poisoned surroundings.

The ordinary appearance of erysipelas at its acme, is a combination of these two processes. Usually (all pieces of skin from infants, forehead of adults) the difference between the process in the cutis and in the hypoderm is very striking, there a pure sero-fibrinous, here a fibrino-purulent inflammation; there the acme already passed, and the number of cocci diminished, here the process still in full bloom. The question arises: is this distinction simply a topographical one, or is the streptococcus of erysipelas actually sometimes weak and sometimes strong in its chemotactic action on leucocytes? In this connection it is right to compare the same process on those parts of the skin, where only a scanty subcutaneous tissue and no panniculus exists, and where that gradually passes into the cutis, and thus is firmly adherent to the parts beneath, *e.g.*, on the skin of the nose and the ear. Here the distinction in the inflammatory relation of the layers is much less. In the skin of the ear and nasal cartilage one sees very well the distension and dilatation of the veins, the white and fibrinous thrombosis of the arteries, and the infarcts of the lymphatics with masses of streptococci and leucocytes, and these may be followed in the loose tissue close down to the cartilage. In this subcutaneous tissue the collection of leucocytes is certainly here and there considerable, but it never reaches the height which it does in the panniculus adiposus. There also extend, here and there, nets of fibrin through the whole height of the skin and subcutis, from epithelium to cartilage. Enough, all the symptoms which are distinct on the fatty skin are found here combined, with distinct predominance of the fibrinous ones.

Consequently it appears to me that the difference between cutis and subcutaneous tissue is really caused by topographical differences. It is not necessary to assume a different chemical activity of the streptococci in different places. One has only to think that a slight leucotactic action of the streptococci is present in the cutis, but that it only extends so far, that the leucocytes escape from the veins and capillaries in quantities somewhat over the normal, and return into the lymph vessels, without saturating the whole cutis and all the lymph spaces filled with cocci. The direct escape from the lymph vessels of the skin is, notoriously, only limited. A number of lymph vessels communicate with the lymph spaces of the subcutaneous tissue, and here end blindly on the walls of the larger blood vessels, others accompany the lymph vessels of the hypoderm. In both cases the whole quantity of leucocytes, escaped into the lymph spaces of the cutis, gradually streams in this direction, and so it happens that the cocci in this place are embedded in masses of pus, although only few leucocytes have locally left the circulation. Although all the pus of the skin collects

here, the streptococci find this, at least for a time, the most luxuriant medium for their growth.

If this explanation of the different appearances in the cutis and in the hypoderm is correct, an erysipelatous inflammation must not be viewed as purulent. The leucotactic action of the streptococci is very much less than that of the pyophoric staphylococci, and since they die off *en masse*, it is possibly only related to their death. They are not, like the staphylococci, the *true* pyococci, everywhere definitely surrounded by a wall of leucocytes, but only in places where the circumstances are more favourable to the stagnation of leucocytes. Here, in distinction to the staphylococci, they regularly penetrate into the leucocytes, which, under the influence of the streptococci, much more rapidly break down than under that of the staphylococci. The third and most important distinction between the two kinds of cocci lies in the much more *rapid and easy locomotion* of the streptococci. Thus they are the cause of spreading inflammations. To the absence of a dense, opposing, leucocytic wall, I cannot ascribe so much importance, for where this chances to be present, the streptococci grow through it without difficulty. Only the form of their colonies is altered; they are broken up into single collections and distribute themselves in and between the leucocytes. But as they do not perish in the leucocytes, they meet with no serious delay.

Very marked was this great difference in the relation of two kinds of cocci in certain furuncular areas, which I found on the skin of the nose. Here there were seen, with a low power, round and elongated areas of nuclear masses in the cutis and subcutis, each of them regularly surrounded by a cloudy zone. Closer investigation showed that these were transverse and oblique sections of lymph vessels, distended and packed with leucocytes; the nuclei of these white thrombi were well preserved, but the protoplasm of the leucocytes had gone, and the inter-nuclear coagulated substance was permeated by scattered collections of streptococci. The peripheral zone was formed of a cloudy mass of collagenous substance, into which leucocytes and cocci from the central lymphatic had wandered; the latter were abundant but small, badly stained and evidently dying. In contrast to the staphylogenic furuncle of the cutis, which shows in the centre well-preserved staphylococci, surrounded by dying leucocytes, and further out by a broad wall of well-preserved leucocytes, the staphylococci were here present in all zones, indeed mostly in the periphery, while the leucocytes were closely collected in the centre. Here then we have the opposite condition: a coccal wall around a leucocytic centre, a pronounced centrifugal distribution of the streptococci. The clouding of the collagenous tissue which contains the dying streptococci

is evidently connected with an extensive thrombosis of the blood vessels and consecutive necrosis of the surface of the skin; here also there was death of the *free lying* organisms, *surrounded by very few leucocytes.*

Still another unusual appearance of leucocytic and coccal distribution remains to be described, which represents the second form of the erysipelas vesicle; *Impetigo streptogenes.** In fatal cases of erysipelas the horny layer was found elevated in many places in the form of the vesicles, and permeated microscopically by innumerable quantities of streptococci. The erysipelas of the cutis had nearly run its course, the collagenous tissue showed, in the most typical way, the partial softening and loosening which has been described, and still, here and there in the dilated lymphatics, a few collections of streptococci. Quite independent of this deep inflammation were the impetigo-formed areas of inflammation of the surface. In contrast to the staphylogenic impetigenes, they were not preferentially arranged at the mouths of the follicles, but were only occasionally perifollicular. But most of them had in their centre a sweat pore, and they had grown down into it as far as the level of the cutis, which I have never been able to determine in the staphylogenic impetigenes. The rest of the duct and the gland were free from cocci. It was then in no way a separation of the streptococci by the coil glands, for these, even in the centre of the severest erysipelas, show no immigration of cocci.

One can further distinguish in the vesicles, free and periporal impetigenes. In the former the leucocytes collect in the horny layer, in the latter around the sweat pore, which at the same time is transformed into a cornified conical plug. They are not present in such numbers, nor in the acute manner of the staphylogenic impetigenes, where the exudation consists of a drop of pure pus, but they permeate the prickle layer in different directions, and the contents of the vesicle enclose many collections of detached prickle cells. In this connection impetigo streptogenes rather resembles the acute eczema vesicle, and the resemblance is greater, since the cocci everywhere penetrate into the leucocytes, which here also gradually break down. For a time I regarded them as vesicles of true morococcal eczema, but there were no characteristic mulberry groups in the horny layer, and the enormous number and regular distribution in the horny layer was unusual; further, there were here and there found distinct chains of three, four, and five cocci, and finally—very different to the eczema vesicle—an unopposed penetration of the streptococci into the base of the vesicle.

* In view of the novelty and importance which the correct diagnosis of streptogenic impetigo coming from without possesses, as opposed to the erysipelas vesicle, impetigo streptogenes is here again described as a complication of erysipelas, although it has been previously described as an independent disease.

In this, impetigo streptogenes differs both from impetigo staphylogenes and from the eczema vesicle, and it is interesting to compare the three affections in this connection. The morococci never burst through the base of the vesicle into the cutis, the staphylococci only where, in a fissure between hair and prickle layer of the hair follicle, a favourable opportunity is given them; the streptococci, on the contrary, grow unopposed in many places through the prickle layer of the base of the pustule into the cutis, in opposition to the moderate ascending stream of leucocytes. Here also, in the papillary body, they are mostly enclosed in leucocytes. In some places we find the streptococci, which have come from above, in the dilated lymph spaces of the byegone erysipelas of the cutis, it may be along with streptococci which have remained there; but in view of the whole spread of the process it cannot be maintained that the impetigenes represent a breaking through of the erysipelas. They are evidently first developed, after the streptococci have accidentally found favourable conditions of nutriment on the surface of the skin, which is certainly not frequently the case. The impetigenes penetrating undisturbed into the cutis from without would not only lead to the formation of furuncles, but also once more to spreading fibrinous inflammation. Otherwise they appear to heal rapidly; many of my (fatal) cases were already cut off by the horny layer and healing, during which the number of streptococci in the crusts appear still to increase.

If, after this discussion, we look back on the disputed question, our standpoint is pretty clear; we cannot admit a strife between leucocytes and streptococci on the human skin; for the cutis it need hardly be considered, and in the subcutaneous tissue the streptococci immediately overcome the leucocytes, for they always break down and die before the cocci. We must, therefore, completely agree with Baumgarten.

As to the other question, whether spreading phlegmon is an affection quite distinct from erysipelas, for which we must assume another cause, the question during our examination took a new aspect. We indeed find, even in ordinary erysipelas, that the hypoderm is more saturated with leucocytes than is generally believed, but we could not establish the diagnosis of a true subcutaneous suppuration along with cutaneous erysipelas, for the masses of pus are mostly displaced into the hypoderm, not, as in subcutaneous furuncle, recently immigrated. If one lays weight on the word phlegmon, then every erysipelas is phlegmonous erysipelas.* Now the deep-lying collections of pus are absorbed in most apparently superficial erysipelata, without our being

* In the following section (progressive phlegmon) it is clear that even the phlegmon, which does not begin with erysipelatous appearances, must be considered as erysipelas.

aware of them, and the cocci perish with them. But where this does not occur, where the cocci do not perish and the suppuration finally become manifest, then we speak of a phlegmonous erysipelas or a phlegmon secondary to erysipelas. So far, then, I am satisfied that the erysipelas coccus can certainly produce spreading phlegmon; but, on the contrary, I do not think it is excluded, that in some cases the staphylococcus aureus is present in addition to the streptococcus.* To the streptococci would then especially be ascribed the spreading of the affection, and to the staphylococci, which certainly do not perish in streptococcal suppuration, the profuse suppuration, which is not a property of the streptococcus. In cases of specially profuse suppuration in spreading phlegmon one should bear in mind this possibility. But the staphylococcus aureus alone can no more cause a spreading phlegmon than it can an erysipelas.

Some of my preparations give some indications of the process of healing of erysipelas, and these are practically limited to the disappearance of the cocci, the removal of the leucocytes, and the absorption of the thrombi. When the permeable blood vessels are supplied with normal blood, the epithelial cells begin once more to proliferate, from deep-lying remains. There appear an extraordinary number of mitoses, which at first form a scaling, but later a normal, cornifying prickle layer. The collagenous tissue also takes on again a firmer and denser appearance, but there are still absent in it almost all connective tissue cells and elastic fibres. It thus supplies an excellent material for the investigation of the genesis of connective tissue cells and of elastic tissue, both very enigmatical processes. Here it must be decided whether the cells grow from without into the collagenous framework, or separate themselves from it, and whether the elastic fibres are formed independently or along with the cells.

Only in one single case, from the nose, have I found plasma cells at one spot. It is at once apparent that in erysipelas, with its acute solution of all those none too firm protoplasmic and intercellular substances, there is usually no opportunity for the formation of hypertrophic connective tissue cells. Therefore I believe that this case should be looked upon as more chronic, and there arises the question, whether the proliferation, swelling, and hypertrophy of the connective tissue cells, which usually are not present in erysipelas, or at the most may be seen while it is healing, are possibly to be found in the stationary erysipelas (rhinitis, ulcus cruris, etc.). In this way many statements as to proliferation of connective tissue cells in erysipelas are perhaps to be explained. We shall deal with the question in discussing Elephantiasis nostras.

* Compare the circumscribed phlegmon, in which in some cases such a mixed infection is still more probable.

Progressive Phlegmon Dupuytren; Pseudoerysipelas, Rust.

A doughy œdema which appears with high, usually remitting fever, often ushered in by a rigor, and spreading rapidly from an infected spot (furuncle, healed erysipelas, foreign bodies, wounds, impure injections, the bites of insects, etc.) over the whole body (extremities, neck), while the surface of the skin, unlike erysipelas, is not deeply red, not warmer, and not sensitive to pressure. Very soon the skin becomes hardened, it may be as hard as a board, the folds of the skin are flattened down, the surface is smooth, soddened and yellowish, and the skin is immovably united to the hypoderm. There appear blebs and wide elevations of epithelium, under which the white and red-dotted, coagulated-looking surface of the almost naked cutis appears. After a week the skin becomes softer, but the general condition remains septic, and there are now and again purulent metastases. On the softening skin there appear greyish white, blackish points, surrounded by dark red halos, which are thrown off in the form of decaying tags, from which pieces of cellularly infiltrated fatty tissue hang loose. The cutis is loosened from the fascia in wide stretches, and even the remaining hypoderm is converted into a ragged tissue which only loosely surrounds nerves, large vessels, and tendons. This change of the connective tissue extends into the intermuscular, periosteal, and lymphatic tissue, and muscle, tendon and osseous necrosis, thrombophlebitis, purulent lymphadenitis, meningitis, sinus thrombosis, etc., may develope. Often before this, septicæmia or pyæmia lead to death. The more favourable cases heal with complete adhesion of the scarred cutis with the fascia and the bones, disappearance of the fatty cushion, and diminished motility of the limbs.

In spite of the severe course and the grave prognosis of these cases, they are, on account of their nature, to be placed close to erysipelas, and are probably produced by the same streptococcus. It may be that it possessed from the commencement a greater virulence, or that it attained such on a specially favourable medium. Certainly at the commencement there is none of the redness and tenderness of the surface which distinguish erysipelas, nor the characteristic border; and the absence of these symptoms, which makes the cases look at first so slight, thus makes them doubly dangerous.

But we have learned facts in the histological investigation of erysipelas which may very well explain the different relation of this pseudoerysipelas. It is only necessary that the fibrinous and white thrombosis of the blood vessels and capillaries in the cutis should reach a particular degree, to have as its result the absence of the ordinary redness, and therefore greater œdema, by which the erysipelatous character is completely lost. The direct result of such a severe and wide-spread thrombosis would then be the tendency of the spreading phlegmon to gangrenous destruction of individual round areas of the cutis, which correspond to vessels. In all other and further symptoms the affection is not distinguished from a severe erysipelas, resembling it in the more rapid progress, the main affection of the subcutis, the

brawny coagulated character and the slight suppuration, which first sets in on the death of the cocci, the extension of the process to the intermuscular, subfascial connective tissue, the general sepsis, etc. Progressive phlegmon is, like erysipelas, distinguished by the slight tendency to bleeding, although the destruction is much greater. It is thus characterised as a fibrinous inflammation.

This view, got from the study of severe cases of erysipelas, is completely confirmed in a few cases of progressive phlegmon which I have had the opportunity of examining. The microscopical appearances correspond in the main to severe erysipelas at the height of its development. All the lymph vessels are choked with colonies of streptococci, and all the lymph spaces are filled with them. But the distribution of the leucocytes and of the cocci in the cutis and subcutis is more regular than in erysipelas. The former are not, as in erysipelas, chiefly limited to the hypoderm, but almost equally saturate the under part of the cutis, while the upper part and the papillary body are relatively free from leucocytes. In the phlegmon also we find, at the height of its development, a perishing, first of the leucocytes, then in lesser degree of the streptococci (judging by methyl-blue preparations).

The connective tissue reacts to this invasion just as it does to erysipelas. The collagenous bundles are much loosened and separated, softened, gnawed, and transformed into masses. Spindle cells and their nuclei have largely disappeared; mast cells are never found. The epithelium is not stained; it is washed out, homogenised, mainly a-nuclear, and here and there elevated in blebs from the swollen papillary body.

Only the tissue fluids and the contents of the blood vessels show a definite distinction from erysipelas. While the collageneous tissue never contains the net of fibrin described in erysipelas, the blood vessels are in still higher degree filled with fibrinous thrombi. The arteries and arterial capillaries show almost everywhere complete chains of deeply-stained thrombi, in which staining shows no leucocytes. The veins and venous capillaries, on the contrary, contain, almost without exception, white thrombi, which are surrounded and permeated by threads of fibrin. We have a condition bordering on stasis, not only in the skin but also in the hypoderm. It is clear that on the one hand this difficulty of circulation must favour the emigration of leucocytes, but on the other hand it is also probable that the greater separation of fibrin in the vessels and the greater consumption of oxygen and the collection of numerous leucocytes in the tissue provide conditions which hinder coagulation of fibrin.

Finally, it is evident that such an affection must clinically give the

impression of a white œdema, for the red contents of the capillaries are mostly replaced by colourless fibrinous and white thrombi. In my case even the capillaries of the papillary body are mostly filled with fibrinous thrombi and leucocytes. Spreading phlegmon is therefore only a higher degree of spreading erysipelas. The clinical differences depend solely on the greater or less destruction of the albuminoid bodies of the blood plasma, and changes in the circulation induced by this. It is of course not to be forgotten, that in some cases a mixed infection with staphylococcus aureus may be present; in my case it was certainly not so, for staphylococci were never found in characteristic arrangement, as the centre of a spherical mass of leucocytes.

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(b). *Purulent Inflammations.*

Circumscribed suppuration of the skin, Cutaneous abscess.

General survey: (Impetigo staphylogenes), (Folliculitis staphylogenes), *Furuncle, Abscess, Panaritium, Circumscribed Phlegmon* (Sycosis staphylogenes).

Circumscribed suppuration of the skin represents, however different the clinical appearance, an etiologico-pathological unity, the invasion of the staphylococcus pyogenes aureus (and albus) into the cutaneous tissue. This always takes place from without, through minute lesions of the epidermis or through the unwounded follicle.

When the pyococci, which may remain for a very long time on the surface of the skin between the horny cells, reach the prickle layer through a wound in the horny layer, they lead to the development of a true *impetigo pustule*, without any preliminary serous vesicle. It usually heals by drying up. More rarely, and only under specially favourable circumstances, the epidermic abscess, as the suppuration increases, bursts through the base of the pustule, which consists of the whole prickle layer, though thinned and stretched. Then a few staphylococci reach the cutis, and there is formed around them a cutaneous ab-

scess, a *furuncle*. The much more frequent method, one may say the normal method, for the development of furuncle is the growth of the organism vertically between the horny cells, that is in the space between horny layer and hair shaft. This space extends in all papillary hairs, and also in the lanugo hairs, into a space between the root sheath and the prickle layer of the hair follicle. Cocci which have got here must act in the same way as those which, by a rupture of the horny layer of the surface, have come in contact with the prickle layer of the epidermis ; they have a chemotactic action on leucocytes, and their products mix with the excreted lymph of the prickle layer of the hair follicle. The main difference, which is especially evident in all the strong hairs, is only due to the fact that the marginal layer of the prickle layer of the hair follicle, the follicle membrane, possesses a more active resistance to the entrance of leucocytes than the basement membrane of the surface epithelium. Therefore, in the case of hairs, there is formed a *perifollicular* abscess, more often than a follicular collection of pus, seated between the hair and the prickle layer of the hair follicle, which would correspond to the impetigenes of the surface.

The formation of the furuncle, by means of the space between hair and epidermis, may therefore be divided clinically, as well as anatomically, into two different types, according as the infection attacks lanugo hairs or stronger hairs with thick follicle membranes.

In the former case the appearance of impetigo passes unnoticed into that of furuncle. The pustule extends less on the surface, but all the more definite is a thickening of the nodule in the upper part of the cutis. This furuncle is then, as microscopical examination teaches, always a hair follicle furuncle, a purulent folliculitis. With this the cutaneous suppuration may conclude, or there may be added to the follicular suppuration of the lanugo hair, and much oftener than clinical experience would suggest, other abscesses in the depth of the cutis, which altogether constitute a larger furuncle. The furuncles which arise in this way from lanugo hair follicles always end—in contrast to impetigo—with the formation of a small scar at the seat of the suppurated follicle.

Less simple and uniform are the appearances, if the primary impetigo pustule is seated in the follicle neck of a stronger hair. It is then an exception to what is the rule in lanugo hairs, for the cocci to grow directly onwards in the hair fissure, beyond the follicle neck, with the result, that the leucocytes get between the sheaths of the hair follicle and its prickle layer, and constitute inside the latter an intra-follicular abscess, a "hair follicle impetigo." I have only observed this once in very many furuncles. And, in this case, there still was the difference from a primary folliculitis of the lanugo hair, that the integrity of the

hair sheaths was pretty well preserved, in spite of the penetration of leucocytes. The rule in all strong hair follicles is rather, that a more extensive pustule of the epidermis succeeds to an impetigo of the hair follicle neck, that this then at the *side of the hair follicle* breaks through, and a *purulent perifolliculitis* is developed. The appearances of sycosis are mostly a combination of such impetigenes and folliculitides. But many solitary furuncles also, *e.g.*, of the axillæ, of the Mons Veneris, and of the perineal region, show the same. Of course this form of purulent perifolliculitis may finally go on to total suppuration of the hair follicle, and more easily on the somewhat weakened hairs, than on the usually very strong ones of the beard; only in this case do true scars develope in sycosis.

But purulent folliculitis leads much oftener to the continuous production of small abscesses in its immediate neighbourhood, than to a suppuration of the follicle. In this way develope most of the *large furuncles* on the neck, in the perineal region, in the axillæ, etc. The clinically uniform, circumscribed character of these boils, since histologically they usually consist of a number of smaller abscesses, can only be understood by the simultaneous inflammation and tension of the skin, which is very considerably increased by the stiffening of the œdematous hair follicles in the centre. A more thorough clinical study of furuncle during its development, with this in view, shows us often enough irregular penetration of the perifollicular abscesses downwards.

With such a multiplicity in the method of development of this apparently simple complex of symptoms, we may admit that the determination of spirogenic furuncles, caused by the penetration of cocci through the sweat pores and ducts into the coil glands, has not yet been successful. But secondarily, the coils are very readily drawn into the suppurating process, as are the individual fat lobules of the hypoderm.

Suppuration of the skin takes place along definite routes, namely along the dilated, cellular blood vessels, especially the veins. At all points where the cocci show their activity, there is a dense collection of leucocytes, under whose influence all cellular and inter-cellular structures run together, or, by the softening of the more delicate among them, are loosened from their connection. We find complete liquefaction of large areas of skin, especially in the fat lobules of the subcutaneous tissue, therefore mainly in the relatively thick panniculus of infants and in the fatty tissue of the finger pulp (Panaritium), where the firm outer sheath favours the work of destruction in the depths, and also in other places under the simultaneous influence of other liquefying remedies (mercury, strong reducing agents, poultices,

etc.). We speak in this case especially of abscesses, for the appearances then exactly correspond to those of abscesses in internal organs. But between these cases, the very rare and the ordinary, in which the suppuration only leads to the formation of a "furuncle," there is practically no distinction.

In the latter also there are growths of cocci in the centre of cutaneous purulent foci, which are in connection with one another, and there is usually a number of microscopical abscesses, at whose seat the tissue is completely liquefied. But there are no larger abscess cavities, for the firm fibrillary tissue of the cutis dams up the pus, and it therefore remains everywhere in liquefied portions of the cutis, which as a whole preserves its framework. And if, finally, in some places there is total liquefaction, then the resistant parts, dense collagenous bundles, arteries, etc., are only sequestrated as a whole, and form, with their saturated surroundings, the *hard, necrotic core,* which is recognised as indicative of furuncle. It is not the greater or less production of pus which determines whether a cutaneous abscess will show the type of an abscess or of a furuncle, but the amount of liquefaction of the tissue, and it is for this reason that furuncle shows the demarcation of a firm necrotic core as the usual result of suppuration of the skin, because the firm, fibrillary tissue, especially of adults, only yields with difficulty to the common influence of the staphylococci and the still greater histolytic (Leber) property of the leucocytes. Usually only the looser collagenous tissue, which surrounds the vessels, coils, follicles, muscles, and fat lobules, liquefies, and sequestrates these or any part of the fibrillary tissue which happens to lie among the pus. This uniform view of abscesses and furuncles of the skin, which is not only supported by histological examination, but also harmonises with all the clinical facts, is not in accord with the views mainly held by the clinicians, according to which the tendency to circumscribed abscess formation, the formation of a central necrotic area, which distinguishes furuncle, are explained by the limitation to the follicular structures or the coil glands. Kochmann first endeavoured to distinguish between furuncles of the hair follicles and the coil glands, but histology gives no support to his view. The clinical fact, that furuncle may develope in the depths of the skin, without our being able to follow macroscopically the route of the pus from without inwards, must be explained in some other way than by infection through the sweat ducts. Even those "cryptogenetic" furuncles are always to be ascribed to an infection through the ordinary route of the hair follicle, and these cases of furuncles beginning deep down are only distinguished from the impetigenous perifollicular ones by the fact, that the cocci in their

passage through the follicle neck have not lead to a perifolliculitis. Acne pustulosa (which see) clearly shows us, that a heightened vegetation and slight extension of pus-producing organisms may exist a long time between the horny cells, without producing pus.* Only when an additional hyperæmia, a greasing or some other water-tight covering, or a closing of the follicles by the use of reducing agents (tar, etc.), supply the cocci inside the neck of the follicle with their optimum of warmth (34° to 38° C., according to Lübbert) and moisture, does there suddenly set in rapid proliferation and an attraction of leucocytes into the follicle. The cases of cryptogenetic furuncle are mostly those, in which a long existence of the coccal invasion can be proved; and thus the post-eczematous furuncles supply a large contingent, as do the very prolonged cases of sporadic furuncle on the neck and around the anus. The outbreak of the furuncle is in these cases separated by a long period from the invasion of the cocci. But, as a whole, the cryptogenetic cases are much rarer than those in which the tract of the pyococcus may even be macroscopically observed, and a definite distinction between impetigo pustules, perifolliculitides and furuncles is not possible in any case of wide-spread furunculosis. We have therefore, if we are determined to preserve our comprehension of furuncle, only the choice of widening it to the more general definition of cutaneous abscess, or simply of limiting it to the cryptogenetic abscess formation. I prefer the former, for the latter has neither theoretic nor practical value.

But if the identification of furuncle with folliculitis on the one hand, and with hypothetical primary inflammations of the coil glands on the other, must be abandoned, there is apparently no explanation of the *circumscribed* character of the cutaneous abscesses, produced by staphylococci. But even in this relation, bacteriological and histological facts are sufficiently satisfactory. In contrast to the streptococcal suppuration of erysipelas and progressive phlegmon, in which the fore-posts of the infective agent lie in perfectly healthy parts, the staphylococcal growth is always found surrounded at the height of the disease by a wall of pus cells and necrosing tissue. The pus-saturated, dying area around such a collection of cocci is of considerable size. The most typical pure cultures of the cluster coccus are seated in the centre of the affection, in completely necrotic tissue; a few collections are found scattered in the inflammatory halo, which is packed with white blood corpuscles, but none exist between this and the healthy tissue. This pyococcus consequently possesses a very deleterious, distant action on living animal tissue, it provides for itself

* The horny layer above furuncular skin is beset, over large areas, with numerous staphylococci, which grow, but produce no symptoms.

—like the tubercle bacillus in the caseous foci—the ground for its further advancement out of the affected tissue itself. It may remain for a time inside this necrotic mass, indeed multiply, but it then dies inside its saturated surroundings, from its own excretions. Only the ammonia drops found among its products can have a curative influence on commencing furuncle. This self-destruction in the growth of the pyococcus, by poisoning its neighbourhood, is evidently the main cause and the sufficient ground for the generally circumscribed nature of these affections. It cannot be denied, that when the primary suppuration is seated inside the follicle, the follicle membrane, which for a long time restrains the leucocytes, also explains and leads to the circumscribed character of the furuncle. But a surrounding and encapsuling membrane is not necessary in furuncle, for the simple reason, that it rapidly disappears in the lanugo hairs, and in the stronger hairs for a long time keeps the pus from the inside of the follicle, and because furuncle, in all cases, even when it has a follicle in its centre, extends very much beyond that. We must not forget, that the furuncle is always perifollicular in its early stage, before in certain cases it becomes follicular.

But if the bacteriological character of staphylococcal suppuration tend to limit itself, from whence extend the small cutaneous abscesses into the tissue, whence especially comes the occasional extension of this process? The extension of the impetigenes into perifollicular abscesses we have met with above, as a circumstance which appears along with the extension of the cause into the hair follicle. But how does the growth of the staphylococci advance inside the suppurated cutis? Here, I believe, we must ignore any explanation in the process itself, and turn to the help of external circumstances. Possibly the movements of the skin during the motion of the limbs, and still more the passive movements in washing, drying, rubbing-in of ointments, massage, and scratching may disturb the contents in the microscopical abscesses, and bring the pyococci into contact with tissue still relatively sound; when a further suppuration must immediately result. Clinical observation shows us only too well the dangerous effects of such movements, and the benefit of rest in the healing of circumscribed furuncle.

This survey of the purulent affections of the skin shows that we possess, properly speaking, only in epidermic and cutaneous abscesses, in *impetigo* and *furuncle*, distinct pathological entities. The latter is, on account of its anatomical character, not to be sharply distinguished from the so-called Sycosis, and on the other hand we have frequently, under the clinical diagnosis, sycosis, impetigo of the beard. It is therefore only a return to the long clinically established idea of sycosis, when

we regard it as a special form of coccal invasion of the skin, whose apparently uniform nature only begins on its localisation around a coarse hair follicle. It would be more correct, from the etiological and anatomical aspects, to divide sycosis into two divisions, and to treat the former with impetigo, the latter with furuncle. But were we to treat on these grounds the different appearances of sycosis in a special chapter, we would have to make the same distinction for the purulent inflammation of the lanugo hair follicles. For that division of purulent infections, which stands between impetigo and furuncle, possesses, in contrast to sycosis, a uniform anatomical structure, and if this is not as yet sufficiently familiar clinically, that is only due to the little interest it has attracted. For *purulent folliculitis of the lanugo hair follicles* stands out, clinically, quite sharply from the series of the purulent dermatoses. I have therefore specially to discuss: *Impetigo, Furuncle, Sycosis staphylogenes* * and *Folliculitis staphylogenes.** The "multiple abscesses" of new-born children, the circumscribed phlegmon and panaritium are treated as further important varieties of furuncle.

Furuncle, Furunculosis.

By furuncle I understand a circumscribed cutaneous abscess, which may be —as in infants—chiefly in the hypoderm, or—as in adults—in the cutis, with projections into the subcutaneous tissue. Furuncles usually follow on impetigo or sycosis pustules, purulent folliculitides of the bare skin and the scalp. The development from an impetigo pustule is more frequent than usually believed, for the pustules may be completely dried up before the furuncle is perceptible. According to the entrance point of the coccus, and according to the depth of the abscess which is formed, the appearance of the furuncle is different; if the impetigo pustule is present they point more rapidly, "ripen" more quickly and burst. The perifollicular ones are retained longer in the depths of the skin, grow more slowly and often lead to larger abscesses. The bursting of the perifollicular furuncle no more necessarily takes place through the primarily affected hair follicle, than through the primary impetigo pustule, although naturally it often occurs. On the one hand, this original route of infection may be healed up, and on the other, the suppuration may extend deeply to neighbouring hair follicles. Long-standing, indolent furuncle gradually bursts through a series of neighbouring follicles, after their suppuration, as through a sieve. Those which follow on external suppuration, as well the cryptogenetic furuncles, indicate themselves as such by a circumscribed hardness and a dull pain. As they increase, the two other classical symptoms of inflammation, redness and heat, appear. If spontaneous or artificial arrest take place at this stage, first the redness and then the heat disappears. If the abscess "ripens" all the symptoms increase, until spontaneous or artificial rupture takes place. There then escapes first, and sometimes only, a pure fluid pus, containing cocci. The necrotic parts of the cutis, with or without necrotic coils, follicles and fat lobules remain at first

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* These will be found under the infectious inflammations of the epidermis.

adherent to incompletely necrosed supports, especially to the blood vessels, and are only slowly eliminated later, as a more or less coherent core. Healing with the formation of a scar then takes place rapidly. "Furunculosis" is only the result of the rapid or slow spread of the pyococci from one seat of predilection to another.

As "multiple abscesses of infants" some would give the furuncle of that age a special position and consideration. But they are only distinguished by their tendency to extend in the hypoderm, which, in infants, is much more developed than the cutis. The more moderate appearances of inflammation give them a certain resemblance to the so-called cold (tubercular) abscesses of the skin. In delicate infants, as a result of emaciation, the furuncle becomes flabby and somewhat moveable, and since the cutis over it remains long intact, the resemblance to tubercular processes is still greater. Eczema, general want of cleanliness, and the administration of iodine or bromine are the ordinary predisposing factors in this form, which is most frequently seen in foundling asylums.

Most furuncles begin as impetigo. The simple, very frequent coincidence of a dermal abscess with an epidermal, which, at the level of the papillary body, communicate with one another through a constricted neck, is not sufficient to establish the diagnosis of an impetiginous furuncle. For even after the rupture of any kind of furuncle from within outwards, there is found, almost invariably, over a narrow opening in the papillary body, a wide-spread purulent undermining of the horny layer. Apart from the quite characteristic symptoms, which accompany the rupture of the furuncle outwards, and which will be still further considered (pressure phenomena, congestion), we may definitely decide, from the distribution of the cocci in the accompanying pustule, whether they have penetrated from without inwards (whether the furuncle has developed from an impetigo), or whether they have first secondarily affected the epidermis through a point of rupture. In the former case we find the cocci arranged, as in impetigo, most densely and regularly directly under the horny layer and in the peripheral angles; in the latter case they are, as a rule, sparing and irregular; the horny layer appears to be mechanically elevated over a wider extent than the epidermal coccal vegetation corresponds to.

The penetration of the cocci into the cutis, and the consequent commencement of the furuncle may take place in two ways. Either the firmness of the horny layer or the rapidity of the collection of pus does not permit sufficient extension of the vesicle outwards, and then the pus, pushing before it the prickle layer and flattening out the papillary body, digs into the cutis, and sooner or later penetrates the uncornified epithelium. Or, after an impetigo pustule has existed for

several days, the cocci penetrate deeper into a lanugo hair follicle which runs through the pustule. Then immediately follows a collection of pus around this follicle, not more extensive than the cocci, which are seated inside between the hair shaft and root sheath, but sufficiently extensive to remove the thin epithelial barrier which divides the pustule from the cutis.

I regard this form of penetration of the cocci into the cutis—impetigo pustule, perifollicular abscess of a lanugo hair, follicular suppuration—*as the most frequent method of development of all furuncles.* The direct penetration of the base of the pustule in impetigo is a rarer occurrence. One would have to assume it, whenever, from the impetigo down to the cutis, one found a regular minute distribution of the cocci, and no compact lamellæ or larger cylindrical collections. But where there are present, in the centre of this homogeneous abscess, underneath the marginal papillary body, such firmly compressed coccal cylinders, plates and streaks in perpendicular or somewhat oblique arrangement—and one meets these in most cases—then one is right in assuming the perifollicular penetration of an impetigo pustule, even when not a trace of the structure of the hair follicle is present. In order to avoid mistakes, I further note that the existence of a hair follicle inside an impetigo pustule by no means necessarily shows that a furuncle is added to the pustule. I have convincing proofs of the contrary, in specimens in which hair follicles run through the pustules, without the cocci having found their way into them. If it were not so, furuncle would be much more frequent—as frequent as impetigo.

If the cocci have got into the cutis the furuncle is established, and its further fate depends on the migration of the cocci, which depends on the peculiarity of the affected soil. In adults the cocci remain, in most cases, for a long time in the centre of the cutis, and are surrounded by a wall of pus corpuscles. These come, through all the spaces of the connective tissue, towards the cocci, from the nearest blood vessels. The cocci and the leucocytes at once begin their work of liquefaction, the finer fibrillary bundles disappear, and the thicker ones become smaller and run together. Thus all the lymph spaces of the skin around the coccal focus are distinctly widened, and the spaces which develope are at once occupied by pus corpuscles, so that it almost looks as if pus corpuscles directly took the place of the connective tissue. Soon the zone around the coccal focus acquires, in double stained sections, a marbled appearance, dense, homogeneous, collagenous bundles, loosely surrounded by elastic fibres, regularly alternating with rows of pus corpuscles. Only when these coarser bundles are freely liquefied does the pus infiltration become an abscess. In sections, in which fragments of pus in the middle usually fall out,

this is represented by a cavity into which stumps of connective tissue, clothed with pus, project from all sides, so that the wall of the abscess has an irregular, torn, gnawed appearance. The cocci are always found in the centre, rarely, also, in the periphery of the abscess, most densely in the oldest masses of pus, but never *in* the cells, always between them.

Where the pus is more fluid, a few colonies of cocci are taken off by the lymph stream horizontally, and generally onwards, owing to the movements of the skin, and thus the abscess increases laterally and downwards. So long as it advances in the connective tissue the walls retain their torn appearance, for pus corpuscles stretch readily along all the lymphatics. Only where the abscess finds a temporary edge does it round off and terminate abruptly. This is everywhere the case where it meets definite structures, especially the larger hair follicles, sebaceous glands, muscles, nerves, coils, fat lobules, and larger blood vessels. If the action of the poison is exhausted the abscess stops, and their surfaces, with the infiltrated wall of the abscess, form the margin. If the action of the poison extend, these structures are also infiltrated with pus; but as they longer resist liquefaction, the abscess maintains for a time its sharp border at their outer sides, and its outposts then have the form of the affected structures. The most rapid breaking down is seen in the coil glands, and they present no previous notable changes in their epithelium. The deep-lying sebaceous glands of the longer hairs resist somewhat longer, but not so long as the hair follicles themselves. In them there is distinct shrinking of the fat cells, and a homogenisation of the normal granular appearance, previous to the purulent liquefaction. The arrectors are often stretched to a maximum by the growing furuncle before they yield, and then they form with the corresponding hair a firm marginal wall.*

The furuncle finds more easy conditions as soon as it escapes from the cutis into the hypoderm. The subcutaneous tissue presents no mechanical delay, the liquefaction of the loose connective tissue proceeds easily, and the fat itself forms a good soil. If, therefore, only those furuncles which get into the hypoderm lead to widespread phlegmon, the cause of this is due rather to the conditions of growth of the cocci than to the chemical and anatomical arrangement of the subcutaneous tissue itself.

The invasion of the fatty tissue is best studied on the skin of infants; the wide extension of suppuration in the fatty tissue is almost characteristic of the furuncle of infants. The suppuration, extending either from the pustule or through the unwounded, small hair follicles, at once bursts through the very weak cutis and extends under it on all

* To this may be partly due the great tension in many furuncles.

sides, from one fat lobule to another, so that the connection of such a furuncle with the surface is only seen in a few sections. The coil glands, so far as they lie in the cutis, are simply elevated with it; where they reach into the hypoderm they are infiltrated with pus, but not to any great degree. So that one can by no means regard this furuncle as an inflammation of the coil glands "par excellence," as Kochmann and Escherich do. On the contrary the fatty tissue indicates a widespread, purulent liquefaction. It is infiltrated by pus corpuscles, while the fat is mostly absorbed from the fat cells. These therefore collapse, but the intermediate collagenous tissue and their protoplasm swell up, so that the fatty tissue at this stage resembles mucoid tissue. A proliferation of nuclei, as in simple disappearance of fat, does not take place. These lobules, although swollen and deprived of fat, are still free from leucocytes and contain no cocci. As soon as these penetrate into such a lobule, it is densely infiltrated by leucocytes, and converted, according to the degree of liquefaction, either into a caseous debris or into fluid pus. In the latter case we have the appearance of "multiple abscesses," the former corresponds more to the furunculosis of adults. The caseous fatty lobules remain longer isolated from one another, the liquefied ones immediately run together and elevate the cutis from its underlying base.

In every single fat lobule the cocci are seated in the centre, and are surrounded by dying pus cells, while in the peripheral mass of the pus the nuclei retain their staining power. Since every fat lobule has an independent blood supply, it suppurates of itself, and by its margin may long be recognised. The intermediate connective tissue septa hardly participate in the suppuration, and do not therefore in the drier abscesses lead to an appearance of isolated foci of pus, and in the fluid forms are relatively well preserved.

Certain furuncles on old people and wasted individuals have some resemblance to those abscesses of infants, in so far as here also a stealthy extension of the infection takes place in the emaciated, flabby hypoderm, which oversteps the boundaries of the furuncular inflammation in all directions.

After having considered as a whole the route of the cocci into the cutis and their encapsulation by leucocytes, as well as the termination of both invasions, viz., the liquefaction of the cutis, we must now consider those changes which, at least in most cases, take place at some distance from the infectious focus. In impetigo these are reduced, as we saw, to a minimum. So also is it in a large number of furuncles; the inflammatory appearances outside the leucocytic wall are infinitesimally slight, the process is limited to the formation of the abscess, which then has the external appearance of a cold, indolent abscess, is not

very tense and is pretty movable. This is the case in the furuncles of delicate children and old people, and in badly-nourished skin generally.

But in most furuncles there is a zone of simple serous inflammation outside the central suppuration. The blood vessels as well as the lymph spaces in it are much dilated, and here and there one sees in them coagulated fibrin. There very soon sets in a swelling of all the spindle cells, which, with their processes adherent, run all through the skin as a deeply-stained net. In addition to these enlarged cells, which now and again, though rarely, contain mitosis, the lymph spaces contain leucocytes, whose number increases as they approach the central abscesses. The collagenous tissue is swollen and œdematous, but by no means liquefied as in the abscess itself. The whole periphery has rather the character of a productive inflammation; indeed, sometimes plasma cells are developed. This especially characteristic alteration of the connective tissue cells in chronic infectious diseases of the skin is, at the periphery of the cutaneous abscess, striking enough to detain us for a moment. In the few cases where they are present, the plasma cells are found scattered along cellular vessels in the neighbourhood of the abscess; they never form areas—as, for example, in Lupus. They are mostly very large, excessively rich in protoplasm, round or cubical, and contain almost always only one nucleus. Multinuclear plasma cells, homogenised and giant cells, I have never found. Only good staining enables one to distinguish at once between the simply swollen connective tissue cells and the leucocytes. They cannot exert a liquefying action on the collagenous tissue on account of their small number. And so they are simply a sign, that the pyococci, in addition to their chemotactic action on leucocytes, can under circumstances induce severe productive inflammation. Where plasma cells were present I have always found proliferation of the epithelium in the neighbourhood. They occurred in very circumscribed, slow cases of perifollicular abscess in adults.

It is this inflammatory swelling of the surroundings alone, which usually gives to furuncle the character of the acute abscess; it induces the Rubor, Calor, Dolor of furuncle, and without it the actual nucleus of the affection would hardly give the impression of an "inflammation" externally. But the furuncular process may run its course without it, and simply, as in impetigo, represent a chemotactically induced leucocytic wall. Therefore I placed the consideration of the latter as a constant symptom at the beginning, and the description of the other at the end. Serous inflammation of the cutis is clinically very characteristic of the furuncle in general, but it is not pathognomonic. It is present in different cases, and in one and the same individual in the most

varied grades of intensity, and to it are due the very varying redness, tension, and swelling. It cannot be denied that this distant action of the coccal growth favours the extension of the central abscess; at least it favours the coalescence of abscess foci, previously single. Usually it is only a temporary, painful addition, which, on artificial removal of the central area, immediately disappears. For the inflammatory periphery itself never contains pyococci; these are only found inside the abscess.

Further, the inflammatory swelling is also the factor which gives to the irregularly scattered foci of pus, externally, a uniform, well-circumscribed character. The non-inflammatory furuncles are always less circumscribed and rounded off; the individual small abscesses are more evident. If one wishes to recognise their position inside the cherry to plum-sized, firm, doughy tumour, one only needs to elevate it a little and to compress it. The purulent areas then appear as small, anæmic spots in the bluish red background, usually centrally, but often somewhat laterally arranged.

The large hair follicles play in furunculosis a more passive rôle than is clinically suggested. We see that the pyococci may, under certain circumstances, grow through the whole hair follicle into the region of the papilla, and form dense cultures in the sebaceous glands, without suppuration of the affected follicles. This can be seen on many sections of furuncular skin, for one always finds near the furuncle, healthy hairs, and often in them more typically-grouped pyococci, than in the neighbouring furuncle itself. The simple penetration of the cocci into the follicle is then insufficient to convert them into foci of pus and the origins of furuncle; for that a diffusion of the poison from the follicle into the surroundings is evidently necessary.

On the other hand, in the same sections, we often find appearances which at the first glance suggest typical follicular furuncles. But it is evident that the hair follicles have not burst from inside into the cutis, but are eroded from the cutis, that from the follicle neck onwards they contain absolutely no cocci, and finally there is seen, over the connective tissue furuncle, another more certain point of origin in an impetigo pustule margining the exit of another hair. In a word, suppurating hair follicles directly communicating with furuncles do not prove the existence of a purely follicular furuncle.

If, then, the simple existence of the organisms in the hair follicle is not enough to cause suppuration, but, on the other hand, they definitely suppurate, not infrequently, from the implication in an impetiginous furuncle, there arises the question, whether there are pure follicular furuncles without the intermediate stage of impetiginous, perifollicular suppuration. This I would not answer in the negative,

although—in contrast to the general view that most furuncles are suppurations of the hair follicle—I have only one single preparation showing it. Certainly, compared to the impetiginous perifollicular method of development of furuncle, which is to be regarded as the typical one, they are the exception. Appearances accompany the termination of the furuncular abscess, which one must know in order not to confuse them with the initial stages of furuncle. If a cutaneous abscess project over the surface of the cutis, there is an obstruction to circulation above it and at its sides, which is evidenced in a maximal dilatation of the capillaries and a plethora of red blood corpuscles. At the apex, there is before the rupture a thinning of the collagenous and elastic tissue. The epithelium is converted as a whole into a dry horny-looking membrane, and is then elevated completely and undermined by pus at certain parts of the cutis. Or the pus penetrates the still normal epithelium, and forms microscopic, inter-epithelial epidermic abscesses, which run together and elevate considerable stretches of the horny layer only. Then the cutaneous abscess again gets a bottle shape; but this secondary pustule is distinguished, as already noted above, from the true impetigo, in addition to the folding of the prickle layer, by the absence of regular masses of cocci under the horny layer.

Circumscribed Phlegmon, Panaritium.

From infective foreign bodies, extravasations of blood after bruises, frost-bite and burns, after erysipelas, lymphangitis and phlebitis, there are formed large firm areas in the hypoderm, over which the skin is still movable and not decolorised. Painless at the commencement, they become, after two or three days, as they project over the level of the skin, very painful, the colour becomes bluish red, the temperature elevated, and the surroundings œdematous. In the course of a week the boil swells up to twice or thrice its original size, the surface becomes smooth, shining, and dark red; every movement produces severe deep stabbing pain. Then fluctuation appears. After spontaneous or artificial evacuation of "laudable" pus, the circumscribed phlegmon heals by granulation, leaving behind it a retracted scar.

The circumscribed phlegmon combines in itself certain properties of streptococcal infection (erysipelas, progressive phlegmon) and staphylococcal infection (furuncle). On the one hand, it extends rapidly in the depths of the skin and the hypoderm like the spreading phlegmon (pseudo-erysipelas), and shows like that, only a secondary redness of the surface; on the other hand, the suppuration remains limited to the originally affected part, and produces from the commencement laudable pus like the furuncle. From the latter it is again

separated by its greater size, and the absence of an initial impetigo or folliculitis; from the streptococcal infection by the absence of unlimited extension, and especially by the pronounced pain.

In cases where circumscribed phlegmon succeeds erysipelas, we must undoubtedly, as in post-eczematous furuncle, assume the existence of a mixed infection. The streptococci have prepared the ground, and when their effect is over, the previously inactive colonies of staphylococci induce a limited but energetic suppuration, beginning deep down. Bacteriological analysis favours this view, for in these cases both organisms are very often found. The same conditions may also be present when the phlegmon developes from infective escapes of blood, scabs of burns, etc. But on the other hand, we must consider that bruises, burns, and frost-bites induce such abnormal and probably abnormally favourable conditions for the multiplication and extension of the germs in the skin, that from this alone the difference of the suppuration from furuncle may be explained. Only for those which arise from foreign bodies (splinters), spread rapidly over large areas of the skin and then become limited, I would assume the same origin from a mixed infection as for post-erysipelatous phlegmon. Of the clinical symptoms, the rapid spread, the slight tension, and the pain indicate the predominance of the streptococcus.

Like the acute phlegmon in general, the special form, which has long been known as panaritium, shows two forms of development. It is either a circumscribed localised, abscess-like suppuration in the fatty cushion of the finger and palm of the hand, or a more rapidly extending suppuration with a tendency to develope into progressive phlegmon and inflammation of the tendon sheaths. It attains its special place by its stealthy course, and those other symptoms, which are to be regarded as the results of its development under the unyielding horny layer of this region. The ordinary redness and projection of the surface are absent, fluctuation is scarcely recognisable, tension is very marked, and thus on the one hand an external numbness, and on the other a deep boring pain is induced. Purulent undermining and elevation of the horny layer complicate the appearances.

In certain cases circumscribed phlegmon becomes gangrenous from the addition of anaërobic organisms. There is great pain, the œdema increases, the colour becomes brownish-red, there is rapid softening, and an evil-smelling, thin, discoloured pus, mixed with gas, is discharged. After its exit and the addition of atmospheric air the anaerobic organisms die, and there immediately sets in benign suppuration and relatively rapid healing. In the foul phlegmon we have probably to do with a mixed infection with organisms which are closely related to those of malignant œdema and Rauschbrand.

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(c). *Inflammations with tendency to breaking down of the skin and necrosis.*

Ulcus molle.

By soft chancre I understand a form of ulcer which appears spontaneously only in the pubic region but is inoculable all over the skin, which is indicated by the rapid destruction of the upper layers of the cutis, the profuse purulent secretion and the softness of the walls, which persist during its whole course, and finally by its tendency to scar over, after a shorter or longer time (two to four weeks). Its great infectivity, without simultaneous immunization of its victim, leads to the fact that the chancre readily multiplies, and therefore usually appears at once multiple. One notices a deeply reddened spot the size of a mustard-seed, over which, on the next day, the epidermis is elevated by pus, while underneath it usually already shows a loss of substance the size of a peppercorn, with a yellowish base and sharply defined, excavated, deeply reddened walls. The ulcer usually increases to the size of a pea or a lentil, while the base of the ulcer often extends further than the border, which then appears sharp and undermined. Left to itself the ulcer rarely reaches a greater diameter than two centimetres, but it may often communicate with neighbouring ulcers. There is never a sclerosing of the tissue, as in the syphilitic initial sclerosis, even the scar remains soft.

Ducrey showed that a form of bacillus was the probable cause of ulcus molle, and I have succeeded in recognising it in the ulcer.

In the ordinary course of Ulcus molle there is almost always developed an apparently local adenitis of the inguinal region, whose ultimate rupture is, however, to be attributed to the addition of secondary organisms.

The first stages of the soft sore are best studied on the deeply reddened spots which, in the neighbourhood of an older ulcer, indicate a development of new ulcers. There the epidermis is still preserved in connected layers, but in the centre it is loosened from the papillary body around a spot where a large number of pus corpuscles penetrate the epidermis, including the horny layer. Outwards this pus canal opens into the purulent, infiltrated, softened horny layer, inwards into a small sub-epidermoidal abscess, which is the cause of the commencing

elevation of the whole epidermis from the cutis. The epidermic suppuration is therefore here neither an impetigo, that is, a purulent elevation of the horny layer, nor a purulent liquefaction of the prickle layer. If a pustule should primarily develope, it consists in the *purulent elevation of the whole epidermis.* The prickle cells are not further changed during the process, and simply contain in their spaces abundance of leucocytes.

If one examines the primary fine pus canal in the centre, with proper staining, it is found filled with the serially arranged bacilli of soft sore, which from here outwards penetrate the small sub-epidermoidal abscess in winding lines. They always lie free, and wind through between the leucocytes without being taken up by them.

During this purely leucotactic action at the seat of the bacillary growth in the prickle layer, there are already, further out, characteristic, progressive, inflammatory changes of the surroundings, both in the epidermis and in the cutis. The prickle layer immediately around the pus canal is not thickened and proliferating, but only somewhat œdematous, infiltrated with pus, and it elevates itself as a whole from the cutis. Further out the leucocytic immigration gives place to a considerable epithelial growth, which leads for some distance to a thickening of the whole ridge system. In the cutis all the blood and lymph vessels are widely dilated, but around the small epidermoidal abscesses, the broad band of plasmomatous tissue has developed a broad nodule, reaching down to the hypoderm, which consists almost entirely of typical large plasma cells and encloses enlarged spindle cells. Rows of plasma cells accompany it beyond the vessels, and clothe the coil glands under the node. This is distinguished from the plasmoma nodes of hard chancre even in this stage, apart from the presence of the bacilli, by the absence of thickened, stiff, collagenous tissue, by the maximal dilatation of the blood vessels and the lymphatics, and finally by the presence of sub-epidermoidal abscesses.

As a second stage I would describe that phase of the chancre in which the epidermis over the middle is definitely elevated, when ulceration has occurred, but the base of the chancre is not yet folded and become necrotic *en masse.* The chancre then represents clinically a flat, pretty even, yellowish loss of substance, with sharply cut, deep red borders. Histologically, we find the plasmoma nodule distinctly enlarged on all sides, and at the periphery still covered by a moderately hypertrophic epidermis, which stops suddenly at the border of the loss of substance. In this latter, several (two, three, or four) layers may be distinguished, if, instead of a nuclear stain, one uses a protoplasm staining, which also shows the bacilli (alkaline methyl-blue, decolorising with glycerine-ether mixture or styron). In this con-

nection not only are individual chancres different, but even individual parts of the same one.

We always find a more or less broad, pale zone which, together with a fine outer border of debris, represents the simplest form of the ulcerated surface. In this zone the deeply staining granulation of the plasma cells is lost, and there are found clear dots or only the nuclei faintly stained; the staining power of the spindle cells has also suffered, and therefore the zone takes, with the staining mentioned, a faint, greenish blue tone. From it bluish violet groups and surrounding lines of bacilli stand out very clearly; they extend with their processes deep into the plasmoma tissue and then disappear. At the outer side of the pale zone the rows of bacilli are often parallel to the surface; in the necrotic debris only a few bacilli are present. Evidently the paling of the zone (with protoplasm staining) *i.e.*, the disappearance of stainable substance, is to be regarded as the direct action of the bacilli growing through it; it is the first and most certain, because always recognisable action of the bacilli.

On some parts of the surface of the ulcer a nuclear zone appears between the plasmoma tissue and the clear zone, in which the nuclei of the connective tissue cells are deeply stained, even with simple protoplasm staining. This marginal zone, which owes its existence to a certain degree of drying of the surface, is usually very closely beset with bacilli.

Yet another variety of nuclear zone, a collection of leucocytes, appears at this stage at limited spots, but is more general at a later stage at the *outer* border of the pale zone, and then forms, with the debris lying on it, the free surface of the ulcer. The nuclei of these leucocytes are also deeply stained with the protoplasm stain. There are found in these cases, and also in the still pale parts of the pale zone, quantities of leucocytes which wander through them up to the free surface of the ulcer, before they infiltrate these parts. The layer of plasmoma beneath contains only a few leucocytes; these evidently emigrate from the most superficial capillaries of the plasmoma. Where the surface of the ulcer appears to be infiltrated with pus in this way, the bacilli inside the leucocytic zone tend to be very abundant, but over it in the pale zone they are only in moderate numbers, and they do not penetrate into the plasmoma.

It consequently appears as if the local immigration of leucocytes opposed some hindrance to the advance of the bacilli, *although the bacilli are not taken up by leucocytes.* But the purulent infiltration of the surface of the ulcer in this stage is by no means equally and generally extended, and has therefore no necessary connection with the penetration of the bacillus.

I would describe as the third stage of soft chancre or that of the acme, that condition in which the base of the ulcer is radially folded and the secretion has become more abundant and purulent; the secretion is of course still contagious. The histological appearances show us a loss of substance, which, compared to that of the second stage, is increased, but mainly at the cost of the already present plasmoma tissue, so that this has not extended in comparison with the increase of the ulcer. From the surface, both fissures penetrate downwards, more or less deeply into the base of the ulcer, leaving spherical and tap-shaped parts of tissue, which are mostly arranged obliquely in a radial direction, and give to the base of the ulcer its eaten-out appearance. Deep fissures usually penetrate directly, laterally under the free walls of the ulcer, which are formed of epidermis, and undermine them for a considerable distance; but this is not always the case. The depths of the fissures are more or less filled with the same necro-biotic tissue, which, by its falling out, has induced the loss of substance of the radial fissures, and on these remains one sees that it must have been a dying tissue rich in bacilli. We find there the most developed colonies of bacilli; they are seen in wavy lines, often parallel to the fissures and lying close to them, extending downwards, and we can follow sometimes, in the middle of the plasmoma tissue, along thick chains of bacilli, the commencement of the necro-biosis, which the formation of fissures induces. There can therefore hardly be any doubt, that the radial formation of fissures and elevations on the base of the ulcer have a genetic connection with the radial spread of the bacillary chains from the seat of inoculation.

The elevations, which form the base of the ulcer, show on their surface the changes described above, the paling from disappearance of the plasma cell granulation, the fainter nuclear staining and the penetration with leucocytes, the latter now especially developed. This increase of leucocytic immigration in older soft chancres is undoubtedly connected with the death of the bacilli in the upper layers of the base of the ulcer, for the living bacilli do not necessarily attract leucocytes. As a fact, one sees in well-stained sections, near the surface, a quantity of very badly stained bacilli, while, close to the margin of the healthy tissue, well-stained bacilli will certainly always be met with in quantity.

The whole process of the formation of the soft chancre may be thus stated: through a tear in the epidermis the bacilli enter, and, some of them dying, lead to a small sub-epidermoidal pustule, which is rapidly followed by the throwing off of the whole epidermis. The bacilli then penetrate in radial processes into the wide-spread plasmoma

of the cutis, which is developed very rapidly by their toxic products, and they fold it up, in that, extending in the lymph spaces, they lead to a form of radial necrosis. Even in the persistent elevations they penetrate, lead to necrosis of the tissue, and vegetate chiefly at the border of the living plasmoma tissue, while they perish in the zone which has necrosed and broken down into debris, and thus lead to an immigration of leucocytes. The wandering cells rush, in always increasing numbers, against the invaders, but pass them by without taking them up, and form the purulent secretion of the chancre, in which rags of tissue and collections of bacilli are enclosed.

The repair of the chancre forms the fourth stage, and begin as soon as the virulence of the bacilli diminishes, and the dead ones are eliminated by suppuration. Since the base of the ulcer is formed of a tissue rich in plasma cells and large spindle cells like granulation tissue, healing takes place rapidly. The epithelium rapidly covers what, on account of the loss of substance, is a permanent scar of the cutis.

But this acute typical course is not always followed; there is now and again a delay of the commencing healing, if the injurious cause be not completely removed. The deep fissures of the surface of the ulcer close, the elevations unite once more to a uniform surface, and the necrotic zone on them is reduced to a minimum. But the young epithelium does not grow over them, and the plasmomatous tissue grows and swells under the borders of the ulcer like a mushroom—a prolonged, though weakened action of the bacilli. We find in these cases of Ulcus elevatum single groups of bacilli on the surface, but not the penetrating bacillary chains of the spreading ulcer.

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Ulcus serpiginosum.

The serpiginous chancre is a form of ulcer commencing in the genital region, and in the course of months and years extending in a perfectly concentric manner over a great part of the neighbouring regions of the extremity; it is completely different from the spontaneously healing Ulcus molle, although at the commencement it is not easy to distinguish from it. While in the soft chancre a centripetal healing takes place, in the serpiginous this is centrifugal; the infectious agent in the one case gradually loses its activity, but in the other only at the affected part, while it continually attacks fresh tissue at the periphery, and deeply undermines it. The extending marginal part of the serpiginous chancre always possesses, therefore, an external, deeply undermined

border, and an internal one gradually passing into the scarred centre. The former is firm and thicker than in soft chancre. The losses of substance run, like mines, downwards and horizontally, often radiating from one point of the periphery, so that the latter, cut out like a tongue, remains for a time before becoming ulcerated. Then follows everywhere the scarring, but it is often not complete, so that the central scar again breaks down in many places, and new undermining may again take place. The secretion is less, and much less infectious than in ulcus mole, so that only rarely multiple circles of the serpiginous chancre are present ; where they meet they directly run together. The ultimate scar is firmer than in Ulcus molle.

The excessively chronic course of serpiginous chancre requires another division than that which we have given in Ulcus molle. The first three stages of the latter correspond fairly well with the acute initial period of serpiginous chancre on every newly affected part of skin, and then comes a second, very chronic period of healing. But in fact that does not correspond closely enough with the remarkable character of the ulcer, which, on the one hand, shows the histological symptoms of the former, and on the other, the very different ones of the latter at the same time. If the sections are made perpendicularly through the border in a radial direction, they are always unsymmetrically-formed in this way, and every one comprises the whole story of invasion at the affected part. Every other oblique or tangential section shows only a varying relation of the different pathological changes, from which the relations are not altogether clear. The following description therefore relates to typical radial sections of a mass of material, got from one case of my own, and two others, for which I have to thank Dr Lauenstein. In one of these latter cases, the chancre included the genitals, and with a second circle the upper part of the thigh, in another, in addition to the genitals and the right thigh, a great part of the skin of the abdomen ; in my case, the skin of the scrotum and the pubic region was mainly destroyed ; the whole border of the ulcer was excised.

If we assume that the ulcer extends on our sections from right to left, we have, at the left side of the section, healthy tissue, on the right, scarred skin, which is, however, still much pathologically altered. In the centre there sinks a more or less broad fissure, whose left wall, comprising the most recently ulcerated skin, always falls pretty sharply, while the right wall frequently rises as abruptly, but sometimes only obliquely or quite gradually and interrupted by deep gaps. The former is always wanting in epithelium, the latter—at least invariably in its upper part—is clothed with young epithelium. If the fissure is very narrow, an excoriated and a freshly cornified wall directly meet. At the base the fissure widens, if it is narrow above, to about the same breadth as it possessed at the upper widely gaping ulcer. The base is

much folded and shows several firm taps, between which the necrosis of the tissue leads to secondary fissures downwards and towards the left. Those ulcers, which affect the thicker skin of the buttock and the skin of the leg, always extend deeper than the soft ulcers of the genitals. But in some, the left progressive side of the ulcer has a very similar appearance to the border of an ulcus molle, and—regarded by itself—is not easy to distinguish from that. The ridge system of the epidermis which, some distance from the fissure, was thickened, is once more flattened out, and ends pretty abruptly at the roundish bent angle of the border. The vessels approaching the fissure from the left are converted into broad cords of plasma cells, and even between them we see swollen plasma cells in the connective tissue, which, just before the perpendicular fissure, run together to a uniform, dense plasmoma mass. To the left are found many single sections of plasma cells and cords around the neighbouring coil glands, follicles and vessels. In the fissure itself there appears, inside a pretty broad marginal part, the same necro-biotic change as on the surface of the soft chancre. The plasma cells lose their deeply staining substance, many nuclei become pale, and the intermediate substance becomes œdematous and gets an untransparent coagulated appearance; the whole dying part at the angle is stained a bluish green, the unaffected plasmoma behind, dark violet. Now it is an invariable appearance in serpiginous chancre, and explains its extension, that the necro-biotic marginal zone sends processes towards the left into the middle of the young plasmoma, or, as miners say, horizontal galleries from a perpendicular shaft. In that gallery, which runs parallel or somewhat obliquely outwards to the surface at the left side of the chancre, one invariably finds numbers of the bacilli, which may well be recognised as the cause of the serpiginous chancre, while on all the other parts of the much ulcerated surface they are only occasional or altogether absent. They lie in long twisted chains, more rarely in packets, and are never enclosed in cells. They are remarkably like the strepto-bacilli of soft chancre.* The more faintly stained galleried parts are completely filled by them, and they extend towards the left, right into the unaltered plasmoma, which evidently becomes necrotic from their growth, in the way described.

One of these galleries is always found close under the epidermis, and in it we have the most deeply staining bacilli and the best histological proof of the clinical symptom of the attack of healthy skin, of the extension of the chancre towards the left. But it should be noted that the bacillary invasion always takes place *between* the blood

* Possibly they are identical with them, see below. In general the chains are only single, the individual members somewhat longer ($1\frac{1}{4}$ to $1\frac{1}{2}\mu$), but these slight differences are not absolute.

vessels of the skin, the most superficial attack, underneath the papillary circulation ; there are therefore found, in the persistent tongues of tissue, dilated capillaries close up to the surface and also scattered remains of elastic tissue, while, at the seat of the necrosing galleries, blood vessels and elastic tissue early disappear.

In the same way as towards the left, the primary necrotic fissure sends secondary fissures outwards between the coil glands and into the fatty tissue, by which means are formed the broad tap-like islands of tissue, which reach perpendicularly upwards ; though here also they were preceded by a diffuse plasmomatous tissue. Here also, in the necrobiotic marginal zone of the taps, though not so abundantly as towards the left, we find the characteristic chains of bacilli.

That part of the chancre already described is the same everywhere, and is completely clear and comprehensible in its significance ; it represents the acute commencement of the process, and one has to conjecture the very first commencement, the first formation of the main fissure, according to the plan of the secondary fissures, very much as in the formation of the soft chancre.

Much more complicated and varied are the appearances at the right side of the chancre, where the process has run its course. The changes which precede scar formation are not so many, but the varieties which they combine are very numerous. There are three main progressive changes which are here to be considered. 1. Further plasmoma formation. 2. Fibroma formation. 3. New growth of epithelium (acanthosis). The plasmoma, so far as it is not destroyed by the extension of the ulcer, remains for a very long time as such ; individual areas may even run together in the scarred parts to larger plasmoma masses. These are only separated by later developed fibroma masses, which, by their horizontal position, their numbers of flat, well-stained cells, the complete absence of elastic tissue * and of normal rhomboidal crossing of the fibres, are always easily distinguished from normal tissue. Thus, while the deeper parts of the scarred skin chiefly consist of plasmoma and fibroma masses, in the upper part an a-typical epithelial new formation plays a great rôle, the plasmoma masses are here mostly limited to smaller areas, and the fibroma masses rarely reach so far out, so that the intermediate collagenous tissue returns to the normal or remains abnormally œdematous. But the acanthosis penetrates from above in the most irregular manner, producing epithelial nets, which in their form recall cancer. Still more important in the form of the skin than these a-typical epithelial growths is the covering with epithelium of all the fissures at the right

* There are usually remains, thick short blocks of elastic tissue present in the plasmomata.

side of the ulcer. Thus develope the unusually arranged borders of this chancre and the persistent undermining, fistule formation, and sequestration of superficial lobules of skin.

If we pass from the simple perpendicular fissure described above, and consider the processes as extending towards the left, several things are possible. Either the epithelium-clad right wall remains stationary, while the left continues to advance—then the fissure dilates to a widely-gaping ulcer with folded base. Or the right wall is elevated by the granulating plasmoma growth (which cannot unite with the left wall on account of its epithelial covering) and follows the spreading of the left—then the ulcer remains a simple fissure, but that is certainly exceptional. Or, as the left wall advances and the ulcer increases, the borders send out tongue-like processes to cover over the loss of substance; this is the most common occurrence, showing that the ulcer does not extend regularly, but in single radii, which is indeed the case. Therefore one finds only a few gaping ulcers, but usually irregularly-mined passages, which extend far into the healthy tissue, and are mostly covered by smooth, epithelium-clad tongues. Further, in sections of these parts, not only are the borders covered by epithelium, but it has grown down inside the skin, corresponding to the earlier, superficially lying galleries, parallel to the surface. Thus over wide areas the borders become fistulous, undermined by narrow canals two to five millimeters wide, and these intra-cutaneous, epithelial layers here and there unite with the a-typical epithelial growths, which directly penetrate from above.

The conditions of scar formation are already multiform enough, but become still more so, since the process at the right side of the ulcer has by no means completely lost its infectious character. We have, as well as the three progressive changes, three regressive ones, which are present at different places—(1) primary necrobiosis from fresh, although locally limited bacillary invasion; (2) a superficial suppuration, also limited, and perhaps due to the death of the bacilli; and (3) a well-marked interstitial œdema complicated with hæmorrhage, which affects all parts superficial to the scar, but especially those which are not fibromatous.

The epithelial growth of the fistulous fissures only takes place where the infected necrobiotic parts of the surface are thrown off; therefore these intra-cutaneous passages present a varying appearance of fissures and taps, which may be covered by a cornified, necrosing or suppurating surface. From that, the slumbering bacillary process may again produce necrosing mines in the apparently healed scar, or lead to the complete necrosis of old taps and processes and to their throwing off. And thus a section through the whole marginal part of a

serpiginous chancre comprises a sort of variety show of more or less necrotic, dry, suppurating, œdematous, hæmorrhagic areas, of broad epithelial processes inside the cutis, of cavities filled with horny layers, and of diffuse or areated plasmoma masses and fibromatous parts running irregularly between them. It is thus understood how the apparently healthy zone behind the ulcer remains long swollen and elevated, although pale, and only after a long time gives place to true atrophy and the formation of a scar, and we also understand its clinical obstinacy and tendency to recurrence. In order to familiarise oneself rapidly with these somewhat confusing appearances, one has always to look out the point, where a remnant of healthy skin—*recognisable by normal collagenous and elastic tissue*—meets a plasmomatic and striped necrobiotic part; he will certainly find in the latter the chains of bacilli, and thus the root of the affection.

Now arises the question: Are all these secondary changes to be regarded as still the effects of the first, definitely-established immigration of chain bacilli, when these can no longer be found in the most extensive part of the partly-ulcerated, partly-scarred regions? And further, assuming that the chain bacillus is identical with that of soft chancre, how is it that here a progressive activity of the bacillus persists, while in soft chancre it is spontaneously removed after a few weeks?

The, as yet, insufficient answer to this question must be: either the chain bacillus here present is different to that of soft chancre—and then all the differences could be ascribed to that, although histologically the bacilli show little difference. Or it is the same chain bacillus as in soft chancre, but there is added to the primary invasion a second, which in some supplementary way induces the striking difference in the extension of the chancre. In favour of this is the fact that in two of my cases one and the same coccus was cultivated (almost always in pure culture), and was recognised microscopically in the more advanced parts of the same case and in all the affected parts. It is a pretty large coccus, which is present in groups, free or in leucocytes, and in both cases usually shows diplococci or irregularly-looped or coiled chains, embedded in the necrobiotic and suppurating parts of the scar and the horny layer of the intracutaneous fistulæ. Its diameter is 1 to 2μ, and in cultures one sees definitely the great polymorphism of the organisms, the larger forms becoming ovoid or even bacilliform. In gelatine cultures the gelatine is very slowly liquefied horizontally, without the development of a filter, while the stab beneath retains its fine calibre. In the liquefied gelatine it produces a voluminous yellow deposit, while the unliquefied gelatine takes a greenish colour. It is therefore not identical with the ordinary streptococcus. The purely

saprophytic existence of this, otherwise unknown, coccus is not excluded, but is improbable, since, in addition to it, no other saprophytes and no ordinary staphylococci can be found in the extensively ulcerated surface.

I have never been able to cultivate the bacilli from the serpiginous chancre.

From their constant presence in the most important parts of the serpiginous chancre, I regard this chain bacillus as the actual cause of the disease, and I regard its identity with the chain bacillus of soft chancre as an open question, like that of the ultimate secondary action of the chain coccus described.

Vaccinia.

The vaccination vesicle developes more or less quickly, according to the origin of the lymph (human or animal) and the degree of disposition. After the first inoculation with animal lymph, there appears on the third day, at the seat of the inoculation, and corresponding to its form, a slight redness, and on the fourth a papule. On the fifth day the apex of the papule tends to become transparent, and assumes, as the vesicle extends to the size of a split pea, a mother-of-pearl greyish colour, and shows a dimpled central retraction, of the form of the inoculation. On the ninth or tenth day the contents of the pock, which is now seated on a deeply-reddened, erysipelas-like, swollen base, become purulent and then dry up rapidly, from the centre towards the periphery, into a thick firm crust, rather larger than the original pock, which, on falling off, leaves a deep scar.

The vaccine vesicle shows exactly the same forms of degeneration of the epithelium as the vesicle of variola and varicella; nevertheless its different extension and arrangement supply differences which are sufficiently great, at once to distinguish the vaccine vesicle from both other forms. These may be briefly surveyed.

In the vaccine vesicle, the ballooning liquefaction of the epithelium is very prominent. The covering of the pock shows four or six rows of simple ballooned epithelial cells, both in the middle and at the lateral parts of the vesicle. The covering of the pock is therefore thicker and less elevated than in varicella, and more succulent than in variola, in which it consists almost exclusively of cornified and very much compressed cells. Consequently the cavity lies more in the central part of the prickle layer and is less extended than in the two other processes. The ballooned epithelial cells, which cover the base of the vaccine vesicle, are more frequently multi-nuclear than in variola, but they do not lead to such numerous and large giant cells as in varicella, while the mitoses in the immediate neighbourhood of the vaccine vesicle are excessively numerous. This intermediate position corresponds to the intermediate strength of the vaccine poison,

which does not paralyse the division of the nuclei like the unmitigated small-pox poison, and does not, on the already affected epithelium, increase it to such a degree as the varicella poison.

The frequent presence of ballooned epithelium in the uppermost prickle layer, where the reticulating degeneration chiefly tends to be present, leads to the fact that we have in individual cells the rare appearance of a mixture of the two forms of degeneration, for some of the balloons lying near the cavity appear inside solid, but in their periphery folded, disorganised, eaten out, and dissolved. Either we must assume that in these older epithelial cells the main part of the cell body underwent, from the commencement, the ballooning, and the periphery the reticulating colliquation, or more probably, that already ballooned, older epithelial cells, whose periphery came into contact with the cavity, underwent, secondarily, the net-formed liquefaction. At any rate, from such exceptional appearances one cannot assume a regular transition from the ballooning into the reticulating degeneration. On the contrary, as a rule the epithelial cells only undergo one or the other, without showing any transitions, even if they are directly adjacent. But in general the greater prominence of the ballooning degeneration in vaccinia may be due to the fact, that here even the older epithelial cells have a juvenile character, and are less cornified, corresponding to the tender age of their owners. For the greater development in the cell mantle of a tendency to cornification disposes to reticulating degeneration. We may therefore expect that the vaccination spots of adults (which I have not been able to procure) would in this respect rather show the type of the variola vesicle.

Quite independent of the age of the individual, however, is the most important deviation of the vaccine vesicle, the existence of an inoculation wound. This can be recognised at the upper angle of the section, as an artificial fissure, usually filled with blood corpuscles, inside the horny layer, which is usually somewhat thickened. From this there extends, perpendicularly or obliquely, an epithelial process to the base of the pock, which is shown, by its extremely widespread degeneration, to be the centre of the affection, and the first poisoned part of the epithelium. Even here one recognises the preference of the younger epithelium for the ballooning, and the older for the reticulating degeneration, for the upper part of this cord consists of a dense net of fibrin, which passes underneath into elongated balloons. These latter are certainly only partly recognisable as such. They are almost all a-nuclear and completely fibrinous, so that one may describe them, in Weigert's sense, as a-nuclear lumps.* Certainly they correspond much better to Weigert's drawing than most of the balloons at

* "Kernlose Schollen."

the base of the variola pustule, and than all other epithelium at the base of the vaccine vesicle. Here also the action of the poison leads, indeed, first to coagulation necrosis, and to the formation of a-nuclear lumps, an experimental corroboration of the correctness of Weigert's view, so far as concerns the existence of such a form of poisonous action. On the other hand, there is no ground for regarding the other appearances of inflammation in the pock as simply reactive to this primary necrosis, and not rather as a diminished further action of the same poison. To this latter view corresponds the histological appearance of the vaccine vesicle, where we have at the base of the pock, following on the totally necrotic epithelial cord, first greatly, then less degenerated, then swollen epithelium, and finally, epithelium showing mitoses.

The vaccine vesicle also shows a chambered formation, which, in the disposition of its septa, partly indicates the youth of the affected skin, and partly the varied route of the intoxication. For the septa consist—apart from the definitely formed, coagulated cords, at the seat of the inoculation just described—not of pretty firmly compressed, elongated, degenerated epithelium, as in variola and varicella, but of less altered collections of cells, which partly enclose granular cells, and by their passage into the coil ducts may be recognised as the remains of the sweat pores. These are—like the coil gland apparatus as a whole—especially well developed in relation to the prickle layer in infants, and form the more resistent parts of the prickle layer, which longest resist the poison which extends from the central cord. This difference gradually disappears in children and adults, and the variolous or varicellous poison, which penetrates into the epidermis from beneath, from certain points in the cutis, furnishes, from the more homogeneous prickle layer, according to the accidental interference of neighbouring sources of poison, a larger series of more or less regular regions of compression, which have no sharp relation to the sweat pores, and which, as the colliquation advances, become the septa or rafters of the pock cavity.

In relation to the appearances of inflammation in the cutis, and the later slight suppuration, the vaccine vesicle again rather resembles varicella than variola. The dilatation of the vesicles and the swelling of the connective tissue cells hardly extend further than the papillary body. There is no formation of plasma cells. The emigration of white blood corpuscles is, even in extensive vesicles, very moderate, and even at its height is never so extensive as in variola. Evidently the vaccine poison, like the small-pox poison, can induce independent suppuration ; but there is absent, in the normal uncomplicated course of vaccination, the action of the ordinary producers of pus, which are

always present in severe variola, and interfere with the typical conclusion of pustulation, or altogether prevent it.

The formation of the dimple also distinguishes it from the variola vesicle. Were the vaccine vesicle not produced by a lesion of the epidermis, one would certainly not find any pronounced umbilication, for one of the main factors which comes into consideration in variola, is here very weakly developed, if not altogether absent—namely, the cushion formation, due to severe cellular œdema at the periphery of the base of the pock. The dimpling in the vaccine vesicle consequently depends altogether on another factor, the relatively slight development of the reticular colliquation in the centre, as compared to the periphery. Therefore, in vaccinia we have central umbilication, only because a resistance to the further development of reticular colliquation in the centre is provided by the totally necrotic epithelial cord at the seat of inoculation. So far as concerns vaccinia, with its primary necrosis in the centre and its deficiency in cellular œdema at the periphery, I am consequently completely in accord with Weigert's theory of umbilication, which this author has especially established for variola.

Healing of the vaccine pustule takes place by vigorous epithelial proliferation, which elevates the dried up scab, just as in variola. Only, in vaccinia the scab is much firmer and thicker. Since suppuration is never so great as in small-pox, the scab does not mainly consist of pus cells, but more of epithelium, and since the vaccine pustule is developed much more slowly, and reaches a greater size than any single pock, to this is due the greater quantity of epithelial substance, which in the former perishes. The vaccinia scab is therefore seen on sections to be composed of several horizontal layers, which so far correspond to the divisions of the pustule, by showing an upper layer mainly consisting of fibrin and horn, with few nuclear remains, a second, deeper one, with many nuclear remains, corresponding to the epithelium of the base of the pustule, and a third, the encapsuling epithelium, which, compressed, cornified, and full of wandering cells finishes off beneath the very thick scab, and is difficult to distinguish from the connective tissue base of the pock. The margin is only to be recognised by the dilated blood capillaries. There evidently is, in the vaccine scab (in contrast to variola) after the drying of the pustule, a distinct series of epithelial layers, and consequently the pressure underneath the firmly adherent scab on the tissues beneath is considerable, and leads with such regularity to deep excavation of the base of the pock, that is, to the formation of a deep scar, that we recognise it as a sign of successful vaccination. The papillary body is also, towards the end of the existence of the pustule, flattened out or excavated, and the young epithelial

margin extends, under the pustule, over this altered connective tissue margin.

This shows us, that the extent of scar formation is less dependent on the extent of the epithelial degeneration and the degree of suppuration, *i.e.* less on the severity of the local inflammation, than on the intensity and the duration of the pressure, which, from various causes, the cutis undergoes during the new formation of epithelium.

The absorption of the small number of pus cells from the connective tissue takes place in the same way as in variola, by their return to the vessels. Only, in reference to the youth of the subjects, the coil glands play a greater rôle. They are much dilated and twisted, partly filled with thrown off epithelium and pus, being here and there converted into very small abscesses, and this affects not only the coil glands under the scab, but especially those lying at its side. The latter, indeed, often show a remarkable funnel-shaped dilatation of the sweat pore. It looks as if some of the pus cells sought an exit through the dilated coil glands at the side of the scab; but I have never found pus cells in the sweat pores.

The blood vessels close under the scab in vaccinia are fully dilated, a phenomenon which appears everywhere, where the elastic tension of the skin is removed in limited spots, but which rarely reaches such a high degree as here. After the falling off of the scab they soon regain their ordinary size.

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Noma.

An infectious inflammation, rapidly leading to extensive gangrene, which appears especially on the cheeks of children between the ages of three and twelve, and usually following some weakening infectious disease. It commences as a red spot in the neighbourhood of the angle of the mouth, at the margin of the mucous membrane, around which the skin and the mucous membrane become hard and swell up to as much as four times their normal size. The skin around is œdematous and looks as if it had been varnished. The vessels do not bleed on incision. In some cases the primary spot dries up, and gets black, while the affection extends on the periphery with a broad, rosy red, œdematous border. More often the gangrenous skin breaks down into a greyish brown, stinking debris, and there is a deep loss of substance, showing necrotic, yellow, fatty tissue, with reddish black fluid and dirty black debris. In the course of a week the destruction extends to the whole cheek, nose, lips, eyelids, gums, and tongue, without advancing over the middle line.

Winiwarter (page 255) found on repeated examination no special changes, the arteries and veins almost empty, and only thrombosed at the actual margin of the slough, cloudy swelling of the tissue, and a quantity of saprophytes (cocci and bacilli).

Carbuncle.

A local infectious disease of the skin, accompanied by severe general disturbance, which arises from the follicles, and is distinguished by the formation of primary necrotic cores and a tendency to peripheral extension of the necrosis in the subcutaneous tissue. It appears suddenly, with rigors and high fever, on the neck or back, rarely on the face (lips) or the legs ; it is very painful, and appears as a reddened, hot, boardy tumour, four to five centimetres in diameter, and after two or three days shows in the centre a few yellow vesicles. The swelling is elevated, extends peripherally, with a very œdematous halo, to the size of the palm of the hand or more, becoming of a deeper and deeper bluish red, while successive new pustules and yellow plugs, corresponding to the follicles, appear at the extending margin. At the commencement of the second week there appears, in favourable cases, a central suppuration, which, extending from the centre towards the border, eliminates the necrotic core, leaving behind a riddled cutis, while at the border the necrosis still extends in the subcutaneous tissue. Or the whole skin undergoes moist or dry gangrene, after the surface has become brownish in colour and covered with flabby blebs. Only in the fourth week do we have spontaneous recovery, with or without complete loss of the riddled skin. More often sinus thrombosis, meningitis, sepsis, pyæmia, or exhaustion lead to death.

Winiwarter describes the appearance of a freshly divided carbuncle thus :—Skin and hypoderm are enormously thickened, and are converted into a homogeneous, firm, reddish grey mass, dotted with numerous yellowish white, conical, gangrenous areas, reaching to the surface. Between them are dark red, hæmorrhagic infarctions, and dark lines of thrombosed vessels. At the periphery are found isolated, yellow, necrotic foci in the under part of the cutis. Winiwarter's microscopical analysis was not very satisfactory ; there were no pus corpuscles or remains of glands, but only a characterless debris of collagenous and elastic fibres, containing thready and granular fibrin. Like Riedel, he finds the general formation more characteristic, the primary development of the necrotic plug around which suppuration and gangrene develope, and extend further in the subcutaneous tissue than in the cutaneous.

By many authors carbuncle is regarded as a colony of furuncles, and only distinguished from ordinary furuncle by the greater severity of the symptoms. But the differences are quite sufficient to maintain the old distinction.

Against the furuncle theory we have clinically, the rarity of carbuncle in general, compared to the ubiquity of the pyococci which induce

furuncle, especially their rarity in many regions, compared to their great frequency in others, the limitation of carbuncle to mature age, while furuncle especially affects young people, its predilection for the neck and the back and avoidance of the upper extremities, especially the hands and fore-arms, on which furuncle is so common, the onset with high fever, the severe general disturbance, and more than all, the very serious course.

More important for us is the pathology. v. Winiwarter notes the *primary* tissue necrosis, which is followed, some time after, by suppuration, the extensive *fibrinous coagulation* at the commencement, to which the brawny hardness of the swelling is to be attributed, and the *early thrombosis* of the vessels. None of these symptoms correspond to furunculosis, they more nearly correspond to a streptococcal infection. In carbuncle the gravity of the affection is by no means ended in the secondary suppuration, for the necrosis extends peripherally in the hypoderm. Finally, there is no varicty of furuncle in which there is a regular, peripheral, deep extension; the development of the baby furuncles in the hypoderm is quite irregular. Certainly the secondary suppuration, which occurs in most cases, is in favour of the attack of pyococci at this time, and this may explain the cases in which a carbuncle seems to infect other persons with furuncle.

But there can be no question that the ordinary streptococci of erysipelas are not the infectious agents of carbuncle, although, in the development of fibrinous inflammation, vascular thrombosis and primary necrosis, general sepsis and pyæmia, they do show a certain resemblance. But against them we have the fact that carbuncle is always limited by the fascia, never leads to spreading phlegmon and swelling of the lymphatic glands, and we have present the yellow necrotic plugs and the co-existence of brawny hardness with deep red colour; in erysipelas the skin is red but not hard, in spreading phlegmon hard but not red.

There must then exist a special organism for this affection, with which, as with the more exact histological structure, we are not yet familiar.

Anthrax, Malignant Pustule.

The primary effect of the inoculation of anthrax bacilli on the skin, especially of the hands, arms, neck and face, is either an œdematous change of the surrounding cutis, or an eruption of vesicles on a reddened, rapidly necrosing base.

The histology of the first form, *the œdema*, corresponds to the commencement of the second, the pustule, is evident from the latter, and is anatomically the less important form. Of itself, it would come under fibrinous inflammation in the erysipelas group.

The *pustule* developes, with itching and stabbing pains, after a very varied incubation, at the seat of the inoculation, in the course of twenty-four hours. It developes into a flat, red, shiny papule, which extends into an œdematous, firm

nodule, and is soon covered with a series of vesicles or a larger bleb. After twenty-four hours more, these have dried up into a crust, and this depressed centre is again surrounded by a peripheral wreath of vesicles on a hardened red base. Then the whole nodule takes a dark bluish red to black colour, and dries up. If death does not now take place from the general infection, the anthrax pustule is thrown off as a whole, leaving behind it a flat or excavated surface.

We have then to do, as clinical experience shows, with an inflammation at first sero-fibrinous, but which very rapidly leads to necrosis of the tissue, after a specific epidermic affection, characteristic of anthrax, has developed.

I had the opportunity of examining a fresh anthrax nodule of the lip, covered with vesicles, on which the changes are very beautifully shown. The development of the bacillus had taken place in the form of a flat area at the level of and around the sub-papillary vascular net, but only to a limited extent surrounding the neck of two hair follicles. From here, swarms of bacilli penetrate into the papillary body above, and the epidermis. Only very few bacilli are separated from this necrosed colony, either into the adjacent epidermis or cutis, or in the lymph or blood vessels, and these, as the partial or total loss of their basophilism shows, perish. Outwards, even in the centre of the cutis, there are no bacilli evident, but in spite of this topographical limitation the colony is not so small, for the whole cutis is swollen to at least three times its original size, and the bacilli lie so closely that their number must be reckoned by thousands. This collection of bacilli corresponds to the area of infection; it has altered the cutis, by the action of its toxic products, for some distance, and thus produced the primary effect of anthrax, the pustule. There is, in this region, a marked dilatation of the blood vessels and a severe interstitial œdema of the skin and hypoderm, which especially recalls the œdema of erysipelas, for the escaped lymph has in many places formed into fibrinous nets. They differ, however, from those in erysipelas, which cross the connective tissue bundles, since they follow the direction of the collagenous net and lie in its folds. They fill also all the lymphatics and veins of the skin, but the arteries are at this time free from fibrin and fibrinous thrombi. The fibrinous nets penetrate the fat cells, surround the whole subcutaneous tissue, and penetrate into the connective tissue of the underlying striped muscle. Coagulation of fibrin is therefore much more distinct than in erysipelas, almost as severe as in the first stage of progressive phlegmon; there, as here, it produces the striking resistance of the skin, which is not due to the œdema, the excess of blood and the emigration only. While Weigert's method shows very beautifully the threads of fibrin in anthrax, my methyl blue tannin method shows both that and the great richness of the exudation in granular fibrin, which, like dust, fills all the lymph spaces of the nodule, as far as the œdema reaches.

The acuteness of the process is further shown by the collagenous and elastic substances and the connective tissue cells not showing the severe degenerative changes, seen in erysipelas at the height of the process. The collagenous fibrous bundles are only much loosened, split up into finer bundles and individual fibres, and partly swollen. There is never any indication of coagulation necrosis, but one finds in parts of the upper cutis, in the neighbourhood of the bacillary foci, that fibrinoid and hyaloid transformation of the cutis into thin, deeply stained, winding fibres, which show a resemblance to elastic fibres, and which I have described under erysipelas.

The elastin has partly but not completely disappeared, and is in general more faintly stained. The connective tissue cells are preserved, show no progressive changes, and therefore everywhere disappear before the number of emigrated leucocytes. Their protoplasm is difficult to demonstrate, and is no doubt perishing; but the nuclei are well preserved, and, if properly stained, can be distinguished from the leucocytic nuclei. Mast cells are few, small and round.

The greater emigration of leucocytes is a further point which distinguishes this fibrinous inflammation from erysipelas. The emigration is not only greater but more general, affecting cutis, hypoderm, and deep muscular layers alike. Marginal position of the leucocytes and diapedesis in full action can be seen in all the veins and capillaries, even far away from the bacillary focus. But the inflammation still preserves its non-purulent character, for the leucocytes do not run together to form a peri-bacillary abscess, but remain in single foci, and are scattered around the vessels and hair follicles throughout the skin. There is no more a leucocytic wall hindering the extension of the bacilli, than there is a taking up of them by the leucocytes. Whether, in a later stage than is at my disposal, the bacilli multiply among breaking down leucocytes, as they do in erysipelas, I cannot say, but I think it most improbable, for the pustule in human subjects is already dry and necrotic on the second day. At the commencement of the process, where an acute emigration at once responds to the enormous proliferation of bacilli, I have never seen one single bacillus enclosed in a leucocyte, not even part of a degenerated one. There is in my preparations no ground for assuming phagocytosis in Metschnikoff's sense.

But there is a series of other appearances which give us some idea of the fate of the bacilli at this stage. We find, in the veins and venous capillaries surrounding the focus, now and again, a few well-stained, straight rods, which evidently pass directly out of the focus into the general circulation. But they mostly lie inside a dense collection of leucocytes, without penetrating them or their breaking down. At the other side one can see very clearly, at this early stage, the death

of the bacilli at the border of the area. Their basophilic protoplasm is first limited to small divisions of the rod, while the empty parts take up the acid contrast stain, and also cochineal. Then one finds completely empty bacillary tubes, mostly twisted or bent, and having evidently lost the stiffness of living bacilli. Some bacilli then pass into the general circulation, and others perish, but both without the assistance of leucocytes.

While the previous changes show much in common with other fibrinous inflammations, we come now to that tissue alteration which is quite characteristic of anthrax, and which explains the clinical appearance: the so-called *anthrax pustule.* It is a peculiar *œdema of the papillary body,* with consequent vesicle formation. Both changes extend much further than the sub-papillary bacillary focus, almost up to the margin of the nodule. Here they begin simultaneously; both in the swollen papillary body and in the prickle layer there appear small cavities filled with granular fibrin and lymph. In the epithelium these are partly simple dilatations of the interspinal spaces and partly regular colliquation of individual epithelial cells. In the papillary body it is an interstitial œdema of the already loosely constructed upper section of the papilla.

Since the general swelling of the cutis flattens out the papillary body more and more towards the centre of the affection, this œdema does not affect individual papillæ, but the connected sub-epithelial layer which extends continuously over the centre of the nodule, and reaches there an astonishing height. It has sometimes in the centre a greater thickness than the highly œdematous epidermis above it.

The second peculiarity of this œdematous change of the papillary body is a result of its very rapid development. *The margin of the epithelium is* well preserved, and runs, like a fine membrane, in a wavy line over the œdematous cushion of the papillary body. Since the epithelial cavities above this line have run together into extensive flat blebs, and are also filled with fibrin, we have here two fibrinous layers of quite different origin, and lying horizontally one over the other, which can only be distinguished by appropriate stains (*e.g.*, methyl blue tannin method). For—and this is the third histological peculiarity—the acute vesicular elevation of the horny layer, without previous complete solution of the connection of the layers, induces a *simultaneous stretching of all the cavities in vertical direction,* and thus a great resemblance between the vesicular cavity and the papillary œdematous cushion.* On superficial examination the latter appears to be in connection with the vesicular spaces.

* I use this name to distinguish it from the rest of the papillary body and the epithelial vascular cavity.

The œdema cushion is very sharply marked off from the papillary body beneath it, and consists of steep, vertical connective tissue fibres, densely arranged, which, at the upper margin, run together into a sub-epithelial border. Only very few collagenous fibrils bind them horizontally; but they are always filled with a basket-work of fibrin. The persistent spaces, which have also the vertical form, contain, in addition to lymph, granular fibrin and a few leucocytes.

The vesicular space above shows also a vertical system of cavities, with epithelial cords between; thus a partition which, in many spaces, is not unlike the mesh-work of variola. But here every trace of ballooning degeneration fails, and often the reticular is insignificant compared to the simple colliquation and necrosis of the epithelia, which, drawn out into long bands, gradually lose the staining power of their protoplasm and nuclei. The cavities which ascend vertically, almost or completely to the horny layer, are also long and small, and filled with fibrin and lymph; they contain only a few leucocytes.

The development and covering over of these two œdematous layers are quite irregular, only occasionally are both well developed, in others the epithelium, little altered, lies on a high œdematous cushion, in others, again, the last epithelial divisions of the vesicular space are loosened from the connective tissue edge, and a space, monolocular and filled with fibrin, extends between the œdema cushion and the festooned remains of epithelium, which hang from the horny layer. Here, we have a vesicle penetrated by regular epithelial columns, and supported on a small cushion of papillary œdema, there, a scarcely recognisable degenerated remnant is seated on an excessively swollen œdema cushion.

When the surface of the skin is thus altered and broadened, the bacilli immigrate from the sub-papillary main focus; the central œdema cushion especially, is so densely packed with them, that with a powerful bacillary stain it is hardly possible to see any interstitial tissue. In the more peripheral parts of the œdema cushion the immigration of bacilla is less or is completely absent, and in this peripheral portion, which is only filled with serum and fibrin, we see clearly that these peculiar formations are not originally due to the growth of bacilli; no remains of bacilli are found in them. *The clinical extension of the wreath of vesicles on the second day, corresponds to a peripherally extending transformation of the surface of the skin into a papillary œdema cushion*, on which more or less formation of vesicles has taken place. Both develope from the distant action, not from the immigration of bacilli.

But the epithelial vesicles have no immunity from the billeting of bacilli, and there are places in which all the vesicular spaces are densely packed with them. But, on the other hand, not every, and

especially not every recent vesicle contains bacilli. If one has pricked such a vesicle and sought in vain in the drop for bacilli, he should always try a little deeper, in the œdema cushion in the centre of the node.

This fibrinous degeneration of the surface of the skin not only completely corresponds to clinical observation, it is even histologically characteristic of the anthrax pustule. And yet the peculiar structure of the vesicle and the œdema cushion is quite simply explained, if we only think of the abnormal acuteness of the inflammation which results on the local proliferation of the bacilli.

If we take one more look at the other, more dangerous form of the primary affection, the anthrax œdema, there is absent both the formation of the œdema cushion and that of the vesicle. Evidently, here also, the formation of a necrosed area in the sub-papillary tissue, which is closely related to the superficial symptoms, is absent, and it is probably due to the extension of the bacilli in the lymph vessels of the skin, just as in simple erysipelas. The danger of this second primary lesion can certainly not consist in the fact, that in the pustule the bacilli are walled up or attacked by leucocytes; of this there is no evidence. But the well-known (certainly not absolute) benignity of the pustule is solely due to the rapidly developed necrosis of the nodule, whereby the central and superficial bacilli perish, or at least are sequestrated and eliminated. On this, my material, unfortunately, gives no complete evidence, only suggestions which must be later confirmed.

As said above, the separation of fibrin in this affection is considerable, even on the first day, but only in the lymph spaces, lymph vessels and veins. Fibrinous thrombi in the arteries, such as are seen at the height of erysipelas, are absent. But I found in the large subcutaneous arteries, what must undoubtedly soon have led to an extensive arterial thrombosis, namely, a vesicular dilatation of the endothelium with formation of vacuoles, analogous to the reticular degeneration of the surface epithelium. The affected cells are already surrounded by adherent leucocytes. Very probably then an acute thrombosis of the arteries of the cutis, in the course of the second day, is the cause of the rapid necrosis. In favour of this, in addition to the fibrinous character of the whole inflammation, is the fact that the pustule sinks in while necrosing, sometimes indeed dries up altogether.

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Malleus, Glanders, Farey.

An acute, universal eruption, extending in a few days over the whole body, recalling in its appearance a general furunculosis or variola, or a localised dermatosis, not unlike an ulcerating syphilide, extending chronically by the lymph spaces, especially on the face, in the region of the nose.

The former commences with dark red spots, which rapidly swell up into yellow, pustular-looking but solid, soft nodules (farcy buds). These are scattered, but run together from their constant increase, and often show pock-like vesicles on their summits. If death does not at once take place, the nodules burst and form sinuous, undermined, polycyclical, confluent ulcers with yellow base and elevated red halo, which discharge no healthy pus but a thin fluid (farcy ulcer or farcy chancre).

The elementary lesion of the chronic glanders nodule is the same as that of the acute eruption, the yellow nodule appearing on a bluish-red, doughy base which ulcerates without the formation of a pustule and without showing any proper fluctuation. The chronic ulcer extends indefinitely, although slowly, at its periphery, the elevated halo advancing with irregular, torn, infiltrated, steep, more or less undermined walls. The base is irregular, often deeply eaten out, and shows yellow rags of necrotic tissue, surrounded by red granulations. The slight amount of secretion which exudes is not purulent but gummy, oily, and mixed with dark streaks of blood.

Then develope lymphangitic cords and nodules, and elevated swellings and inflammations of the lymph glands, more like erysipelas than phlegmon.

To this unique clinical appearance corresponds an equally unique anatomical one, completely explaining it, which I will describe from the examination of a series of acute nodes. These were mostly quite fresh; some were covered with pustules, while others were in the commencement of ulceration, so that they appeared to me sufficient for comprehending the nature of the process.

We can definitely distinguish three stages of the affection: that of *embolus*, of the *node*, and of *ulceration*, which clinically correspond to the roseola, the nodule with the pustule, and the farcy chancre.

In the first erythematous stage one finds a superficial vessel of the cutis, containing a number of glanders bacilli, peculiarly degenerated. It is four or five times its normal breadth; the endothelium, enormously swollen, shows scarcely any cell margin, and except for narrow spaces filled with fibrin, and showing a few leucocytes and bacilli, fills the whole lumen. The cell bodies have run together to a tangled, fine, thready necrotic mass, which, rather remarkably, stains equally in acid and basic colours. In spite of this deep staining, one sees definitely that the nuclei have not undergone the same degeneration, but one of their own; a number of chromatin balls or drops lie scattered about in the necrotic tissue, and only a few broken-up, irregular nuclear remnants show the site of the original nucleus. In some places one

sees these necrotic vessels, which run through otherwise normal connective tissue, and are margined sharply on all sides by well-preserved elastic fibres, surrounding themselves with a mantle of necrotic connective tissue. This further extension is evidently dependent upon the escape, it may be the growing out of the bacilli from the vessels into the neighbouring lymph spaces, where one now finds them round about the vessel.

In contrast to the vascular endothelium, the bacillary poison produces, in the epithelium, the more distant connective tissue cells and the collagenous substance, a necrosis which is characterised by the fact that the product will take none of the ordinary stains for protoplasm and intercellular substance. Therefore the dark-stained vascular streaks lie in a relatively clear space, which, like the endothelium, is only permeated by deeply-stained chromatin drops and nuclear remains. Since this peculiar nuclear degeneration plays a great rôle in the ripe farcy buds, and as yet does not appear to be sufficiently separated from other forms of nuclear degeneration, I will call this melting of the nucleus "chromatotexis." It is not pathognomonic of glanders, it is found also in other necrotic processes, though never in such high degree and so invariably as here.

If one applies very powerful acid stains (orcein, acid fuchsin, water-blue), one sees that the perivascular necrotic region has a collagenous scaffolding, developed from the splitting up, rarefaction and *colliquation* of the collagenous bundles of the cutis, and, as a whole, represents a coarse-meshed, irregular, œdematous net-work, penetrated by large lymph spaces. The elastic substance has suffered less, and frequently surrounds the free spaces of collagen and cell protoplasm. Where one has to look for the vanished portion of collagenous substance and the cell bodies, is not easy to say. Probably we find them again in an indistinct mass, which stains a faint grey with hæmatoxylin, and green with methyl blue, and, along with the nuclear fragments, partly fills the spaces in the remaining collagenous scaffold. This necrotic vascular mantle shows, outside, no reactive zone of cellular hypertrophy as in the other "infectious granulomata." The action of the glanders bacillus evidently does not reach much beyond the place of its growth. Nor is there any intimation of a local leucocytosis; the bacilli appear to be chemotactically indifferent to wandering cell. Further, it is not unimportant to note that we have here an example of rapid and energetic exclusion of a large capillary region of the skin, which, neither before nor after, shows anything but traces of diapedesis of red blood corpuscles.

From these perivascular foci there now develope the yellowish,

prominent nodules of the skin. They consequently correspond to a vascular cone, and are either more superficial and lentil-formed, or deeper and then almost circular, look as if stuck into the healthy skin, and therefore appear still more sharply margined microscopically than macroscopically. For the clinically evident, bluish-red zone is seen, microscopically, not to be in the least necrotic but only hyperæmic. The surrounding capillaries, arterioles and small veins are all much dilated, as are the deep vessels at the subcutaneous border of the skin, to which the darker shade of the hyperæmia is due. The perithelium of these vessels is formed of large, partly rounded spindle cells, but they show no transformation into plasma cells, as on the peripheral vessels around lupous and syphilitic nodes. Mast cells are present but are not increased in number. The contents of the dilated vessels consist, in addition to erythrocytes, of a very moderately increased quantity of leucocytes, which have no marginal arrangement, and thick threads of coagulated fibrin. There are no bacilli.

The glanders nodule itself is striking in its homogeneity. Yellowish and cloudy in unstained preparations, it is in well-stained ones much clearer than the surroundings, but densely sprinkled with chromatin fragments, and here and there are darker streaks and circles, sections of necrotic vessels. Let us now follow the individual constituents of the skin from the healthy surroundings into the nodule.

The well-stained collagenous bundles of the neighbourhood pass, at the margin of the nodule, into a rarefied and much more faintly-stained basketwork, which, towards the centre, and especially towards the surface of the nodule, shows larger and larger spaces, and finally no longer stains. Only the thickest bundles extend a short distance into the nodule, and they retain their colour and shape. The elastic tissue is better preserved, and if well stained can be followed through the necrotic region, although it is more faintly stained than normal. But it undergoes another metamorphosis, for the fibres partly run together into round groups and clumps. These drop-like masses of elastin resemble the chromatin balls already described, but may be very easily distinguished by their brown colour (in orcein-hæmotoxylin staining) from the blue chromatin derivatives. The cellular substance of the connective tissue cells completely disappears in stained preparations. . Here, too, a formless, homogeneous, gelatinous or cloudy substance, only faintly stained by the most powerful re-agents, occupies the place of the vanished collagen and protoplasm. But the endothelium of the blood vessels persists, even here, as a felted, easily stained mass. Around them, large lymph spaces have formed, so that they stand out from the rest of the necrotic tissue, and in sections

may drop out, so that we may speak of a *dissecting necrosis of the blood vessels* of the glanders skin.

The fate of the nuclein in the nodules is of great interest. The different appearances can only be explained thus :—Firstly, that no chromatin is lost by the toxic action (the mallein acts as an acid, not as a base), for if there were there could not be, in the absence of primary new formation of nuclei, such quantities of altered chromatin ; and, further, that the chromatin passes into a semi-solid, exceedingly plastic condition. For here it exists, not only in the form of globules and drops, but especially in the form of elongated, twisted and bent threads, which always terminate in chromatin drops, at one or both ends. The whole necrotic region is penetrated by such chromatin threads. Sometimes they show extraordinary forms, but these are always seen to have spherical surfaces or elongated points, something like what is formed when melted metal or glass is dropped into water. There can be no doubt that, in the solution of the cell substance, the liberated chromatin of the nucleus, acted on by the lymph stream, passively takes these forms. The elastin balls seem to be much more resistant. (Front., Fig. 15.)

What makes the recognition of these chromatin threads in the necrotic area especially important, is the fact that they are so easily confused with glanders bacilli, for both substances usually take the same stain. When a chromatin thread is very long and thin, and broken into several fragments, it often resembles, in methyl-blue preparations, a row of bacilli. But the tracing of such threads into nuclear drops or fragments, their expansion in their course, their striking homogeneousness, and their rounded ends, on the one hand, the regular calibre, the coccothrix-form of the rods if properly stained, and their sharp, not rounded ends, on the other, are always sufficient to differentiate them, as does a contrast stain. And further, with good, old, basic methylin-blue the colour of the bacilli is never exactly like that of the nuclei and nuclear drops.

The most important constituent of the nodule is of course the bacilli. These are notoriously difficult to demonstrate, especially with a contrast stain. On the one hand, this depends on the slight fixation of the basic colours in the bacilli, and on the other on the richness of the nuclei of the nodule in chromatin. We must therefore endeavour to diminish the staining of the latter, which may be done by glycerine ether mixture or arsenious acid. Then the more successful the process the more evident are the bacilli. In very good preparations the nodule is completely permeated with bacilli, which have in general no definite arrangement, but look like a box of matches emptied on a table, usually they are single, but often two or three lie alongside or in a row, and

according to the method of staining and decolorisation, present smooth, sharply-angled, evenly-stained rods, coccothrix forms, or equally thick bacilli, deeply stained only at the ends, and of varying length. Among these a-typically arranged bacilli, which lie in the spaces of the rarefied necrotic tissue, I found, however, three characteristic arrangements, which develope from the aggregation of the bacilli in pre-existing structures. First come chains of two or three bacilli inside the larger, dense collagenous bundles, which have persisted at the periphery of the nodule. They lie inside the bundle, parallel to its direction, in scarcely visible fissures, and appear to have a preference for this situation. In such places a powerful double stain is most successful (collagen: red from acid fuchsin or orcein).

Then one sees, scattered in many places all over the nodule, shorter chains of four to six rows, which closely fill up the broader lymph spaces. They resemble the short chains of the strepto-bacilli of "ulcus molle," but are distinguished by their being thinner and longer. In cross sections such thick chains look like the mouth of a Mitrailleuse, and we can see that these apparently free chains are really "glœa" forms of the bacillus, in which only the rods appear stained.

Finally, many are irregularly grouped in the necrotic endothelial plugs of the blood vessels.

Evidently the necrotic soil, which the bacilli provide in the skin, is a favourable medium for their growth, so that further proliferation and glœa formation take place, and the bacillary growth is at first limited to a vascular cone. The appearance of isolated roseolæ, which, swelling up, become yellow, doughy nodules, surrounded by bluish red halos, and retain their size in the subsequent ulceration, is easily explained from the histological condition described, viz., the circumscribed necrosis of a vascular cone of the skin, with a reactive hyperæmic zone.

But the degeneration is not limited to the cutis alone. In many places where the necrosis reaches the surface, changes in the epithelium may be already recognised, consisting in great dilatation of the intercellular spaces and reticular degeneration of epithelial cells, especially in the upper parts of the prickle layer. But I have never found bacilli in the lymph spaces of the epithelium; they appear only to reach the surface of the papillary body. This is almost completely flattened out by the combined swelling and necrosis, or is convexly distended in the form of a gently ascending papule. This change of the necrotic papillary body leads to the graver form of epithelial change; the total separation of the epidermis in the form of a bleb. The vesicles of glanders are consequently due to two different processes; sometimes they develope from the confluence of reticular degeneration of the epithelium, sometimes by the total separation of the epidermis; in the

one, a basal layer of prickle cells still adheres to the papillary body, in the other the whole epidermis has become the cover of the bleb; the former are smaller and are usually seated at the border of the nodules, the latter are larger and cover the centre. Even in the latter I have never found bacilli, though of course I have found them on the necrotic surface of the cutis at the base of the bleb.

The epithelial cells resist the poison of glanders much better than do the constituents of the cutis (an important distinction from variola). Their protoplasm becomes œdematous but not primarily necrotic, and even the epithelium of the elevated cover of the vesicle retains, for a long time, its staining power. The nuclei of the epithelium do not undergo chromatotexis, and stain brilliantly. Certainly the lymph spaces of the epithelium are filled with nuclear drops, but, in view of the favourable condition of the neighbouring epithelium, these can only have been washed out of the cutis into the epithelium. It is remarkable that the vesicles contain very little fibrin and almost no leucocytes. In long-standing cases, a few epithelial complexes break up, and then certainly become necrotic, and resemble the necrotic endothelium of the blood vessels, which has been described. It is evident then, that the vesicular eruption in malleus has only a slight resemblance to the variolous eruption; it resembles more the vesicles of erysipelas and anthrax. The vesicles are serous, and their walls gradually undergo the same necrosis as is seen in the connective tissue.

The resistance of the epithelium explains also why it is that, after the rupture of the nodule, the borders usually project far beyond the cavity, and do not extend in the same degree as the destruction of the cutis advances. This rupture is not to be viewed as a suppuration of the nodule, for local leucocytosis plays, although a general, only a modest rôle. The necrotic masses are, from the commencement, soft and œdematous, and, after removal of the epidermis in the centre, separate in fragments or as a whole, as soon as a young granulation from the neighbouring hyperæmic vessels reaches the dead region. Since the throwing off is incomplete, we see at the bottom of the deep excavation, in the subcutaneous tissue, adherent necrotic tags of the peculiar yellow colour. The fluid discharged from such an ulcer is not pure pus, but a lymph, containing a mixture of blood from the peripheral vessels, glanders bacilli, a few pus corpuscles and many necrotic rags of tissue, and, from the presence of soluble derivatives of albumen in the latter, has a gummy character.

The character of the *chronic* nodules may be deduced from this description of the acute ones, for both correspond clinically in their main characters. The more extensive local destruction, which accompanies chronic glanders, corresponds to no fresh histological factor. If

general infection does not rapidly lead to a fatal termination, the individual nodules have time to grow larger and larger. Since the bacilli are in the habit of growing in the lymph vessels, we have the possibility of an unlimited serpiginous extension in the skin, such as distinguishes chronic glanders. The simultaneous extension of the superficial and deep hyperæmia, without the formation of a plasmomatous zone of infiltration, the subsequent irregular excavation of the necrotic cutis, and the rapid breaking down without any proper abscess formation, are all found here also.

But I admit that a conclusion from analogy is no proof, and it must be left to future examination of chronic glanders of the skin, to decide whether there exist no other differences between the two processes than the embolic exanthematous method of development in the one case, and the serpiginous local infection in the other, may induce, or whether in the chronic form there may possibly be proliferative or other inflammatory or necrotic processes.

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Actinomycosis.

Actinomycosis very rarely affects the skin primarily ; in most cases it is secondary to disease of subjacent organs, especially of the jaw-bones, vertebrae, &c. Thus it attains on the skin a certain resemblance to so-called scrophula—*i.e.*, secondary tuberculosis of the skin. It consists in a slow but persistently extending process of softening in the subcutaneous tissue, which, after infiltration and softening of the cutis, bursts outwards in the form of fistulæ or flabby ulcers with widely undermined borders, and keeps up a constant suppuration. Externally, the fistulæ represent bluish red, soft, irregular tunnels in the skin, and are embedded in a firm infiltrated tissue. The fluid is more purulent than the secretion of scrophulous fistulæ, and contains the well-known yellow granules of the actinomyces. The case, from which the following description is taken, was an extensive fistulous penetration and undermining of the skin of the back, extending from an actinomycosis of the spinal column.

Histological examination shows that the resemblance between the cold abscesses of secondary tuberculosis and actinomycosis is only very external. Certainly the coarse anatomical extension of the foci is analogous, the process extends along the subcutaneous lymph vessels in the fatty tissue itself, or at the margin between it and the cutis. But the nature of the degenerations is quite different. In place of the production of dry, caseating masses of cells, we find, from the commencement, a softening of the cells and intercellular substance, in place of an obliteration of the blood vessels in the centre a multipli-

cation and dilatation of the capillaries; finally, the fungus induces suppuration at once; it belongs to those organisms which have a chemotactic attraction for leucocytes.

The degenerations in actinomycosis have a special ground for interest. They supply very clear and convincing proofs of the doctrine of the distant action of germs. While in those infectious dermatitides, which are caused by cocci or bacilli, we are often in doubt whether the products of degeneration, which are present at a distance from the main focus, are due to its distant action, or whether they are locally induced by single invisible organisms, such a doubt is not possible in actinomycosis. There, the well-known rosettes are seated in the middle of the fistulæ, there is no possibility of a detachment of single parts of these compact foci, and yet the connective tissue of the skin is disorganised in a specific manner, for a considerable distance. It is of importance, especially in connection with rhinoscleroma, to study this degeneration zone around the actinomycotic foci of the skin; for in both cases we have to do with the local conjunction of excessive *colliquation and hyalin degeneration of the conneetive tissue cells.* (Front., Fig. 17.)

The basis of this zone of degeneration is formed here also by a collection of plasma cells, and this represents at the same time the most peripheral zone of branching, communicating collections of pus. The plasma cells develope, as usual, by preference, from the perithelium of the blood vessels, around which they are arranged in several rows, and also from the intermediate connective tissue cells. Although constant suppuration is going on in the centre of the area, there are no leucocytes at its periphery, and these therefore have certainly nothing to do with the development of the plasma cells. The layer of plasma cells forms a pretty complete, closed, but relatively thin shell round the actinomyces, then it undergoes degeneration, and the degeneration zone, which constitutes the middle zone of the collection of pus, becomes as much as ten to twenty times broader. The appearance of the plasma cells is also, from the commencement, peculiar, indicating rapid degeneration, for, even with the most careful staining, while they present deeply stained, round or oval, sharply-margined cells, with the well-known perfect oval, coarse granular nuclei, they have only very finely granular protoplasm, indeed it is often almost homogeneous. The spindle cells of this peripheral reaction zone are swollen, but not increased, and no new formation of fibrillary tissue takes place. Very few mast cells are present.

The degeneration of the plasma cells takes place in two divergent directions, but the initial stage is the same in both. The cells swell up somewhat, and lose their sharp, regular contour and their baso-

philism, in favour of an increasing acidophilism. On account of this latter circumstance, we see both degenerations best on those sections which are stained with alkalin methyl-blue, and differentiated with tannin and acid fuchsin.

The still unchanged plasma cells retain their dark blue colour, those which are somewhat degenerated have, on the contrary, a bluish or a rosy red, and as the degeneration advances, get redder and redder.

But now appears a fundamental difference: the protoplasm of the greater majority of cells is dissolved, while that of a smaller number becomes increasingly denser and more shining. The colliquation of the connective tissue cells is a process which is closely related to the reticular degeneration of the epithelium in vesicle formation. Only rarely does it begin with a regular softening of the cell body, which then becomes more distended, more faintly stained, and finally transformed into a mixed up, faintly granular, homogeneous mass, which occupies three or four times the space of the original cell. Colliquation usually begins with the appearance of clear, non-stained vacuoles in the plasma cells, which rapidly multiply, increase, and run together. The very much distended cell then shows a very delicate, faint red-stained, net-like scaffolding, which is certainly rarely so regularly formed as in the colliquated epithelium. In both forms of colliquation the cell mantle shares in the softening process, but there is often preserved a ring of protoplasm enclosing the nucleus; this also takes the red stain. The completely liquefied cells are partly removed by the lymph stream; the nucleus, however, usually remains in its place, surrounded by the small dense ring and a remnant of loose protoplasm, which clings to it like a thin veil.

The hyalin cells also swell to increasingly large forms; but they invariably retain their shape, are oval, and seldom go beyond 20μ in long diameter. We can best observe the transformation of the contents of the cell into a hyalin mass, on sections which are treated with acid fuchsin and tannin or gentian violet, iodine and anilin, or still better, with both stains consecutively. In the latter case one has both red and bluish violet parts in the cell body; the latter corresponds to the more degenerated firm parts, while the red-stained part is the less firm substance. Such cells consist, then, of an oval, homogeneous, red mass, which usually has, at its pointed pole, the well-stained (blue) nucleus, and inside a smaller or larger bluish-violet ball. As the degeneration advances, the whole, still nucleated cell takes the violet colour, and already shows a large series of regular cracks, which indicate the breaking-down into hyalin bodies. Finally, the cell breaks up into a group of transparent portions of different sizes, which at first are still

angled, but which, after being set free, take a spherical form, and as such lie free and loose in the tissue. In many places one finds a collection of blue hyalin globules, which correspond to the original cell. But many of them are washed away singly.

Both forms of degeneration affect only the protoplasm, not the nucleus; that is only lost mechanically by the complete solution or the rupture of the cell. For a time one can recognise distinctly the origin of these cells from plasma cells by the typical oval form of the nucleus and the smaller chromatin granules which distinguish it. Finally, the nuclei also alter, they become smaller, and their chromatin is more packed together, or they break down into two or three smaller, deeply-stained, round granules.

The distribution of these two forms of degeneration inside the middle zone varies in different places. Sometimes they directly alternate, so that every hyalin cell is surrounded by a number of liquefied ones. Often enough we find numbers of liquefied cells with very few hyalin ones, in other places the reverse. Indeed, in some points, the hyalin cells are so densely packed that every other tissue appears to be absent. They lie here almost as closely as the hyalin epithelial cells in epithelioma contagiosum, to which, in their regular size and oval form, they present certain resemblances. At these places the number of hyalin cells is still greater than in rhinoscleroma, and far more than in the other infectious granulomata.

In this central zone of the actinomycotic area, the collagenous tissue gradually atrophies, undergoing the same liquefaction as the connective tissue cells. We find certain connective tissue bundles broken down into granules, as if worm-eaten, and finally complete splitting up and destruction, with the formation of large lymph spaces in their place. The elastic tissue in the central zone also disappears, the fibres becoming thinned, not staining, and breaking down. Apart from the hyalin cells and clumps, the still well-preserved coarser collagenous bundles and a certain number of spindle cells, the tissue in the middle zone is converted into a semi-solid, soft mass, and the tissue pressure is greatly diminished. To this is evidently due the fact that the blood vessels running through are distended and everywhere filled with blood, though hæmorrhage from them is not characteristic of actinomycosis. But, on the other hand, it is easy to understand that, in the abscesses and fistulæ of the skin of the back, a simple hypostatic hyperæmia is all that is needed to burst the capillaries of this zone, and to convert the centre of the abscess into a pool of blood. Thus the loose, rarefied, central zone, the spongy "abscess skin," has its meshes filled with blood, so that it gives the impression of a hæmorrhagic infarct, although no primary and direct saturation from

bleeding has taken place. On the other hand, there can be no doubt that this saturation with blood has taken place during life, and is certainly not an agonal or post-mortem appearance, for all around the hæmorrhagic abscess areas blood pigment is to be found.

In this area, the degeneration zone, favoured by the bleeding, passes gradually into the centre of the abscess. But where no bleeding takes place, and the normal circumstances obtain, the two regions are sharply separated. The centre of the abscess is occupied by a collection of pus, in which, here and there, the ray fungus is embedded. The pus comes from the dilated blood vessels of the abscess membrane and collects towards the centre, first forming directly around the ray a drop of pure pus. The zone of degeneration, however, in its outer part is quite free from leucocytes, and the dilated capillaries, which are crammed with blood, show no marginal arrangement of the leucocytes. That is only found on a few capillaries directly adjacent to the drop of pus. One must be careful not to mistake the liberated nuclei of the degenerated zone for the nuclei of white blood corpuscles; if the staining is good the distinction is easy. All this shows that the ray fungus, seated in a central lymph vessel or a lymph space, only acts on the leucocytes in its immediate neighbourhood, and produces no general "inflammatory" change in the vessels. This is all the more remarkable, as, around this infectious centre, a broad zone of intense degeneration has developed, and still further out a smaller, progressive inflammatory one of hypertrophic connective tissue cells. Thus this example of actual suppuration of the skin does not lead to appearances, in which the immigration of leucocytes plays an important rôle. It simply serves to excrete the ray fungus out of the degenerated cutaneous tissue.

To judge by the clinical appearances, the pathological process in human actinomycosis is always limited to these lines. Tumour formation, as in the actinomycosis of cattle, does not appear to develope in man, although the foundation of it is found in the peripheral zone of plasma cells. By this very slight and transitory formation of plasma cells, and the absence of new formation of fibrillary tissue, human actinomycosis is clearly distinguished from rhinoscleroma, with which it strikingly corresponds in regard to the cellular degeneration. A greater development of the outer zone of plasma cells, which no doubt might develope, would at once give to the affection a more tumour-like character.

I can, so far as concerns my case, definitely exclude a mixed infection, which Baumgarten assumes to explain the suppuration in actinomycosis, for the methods used to demonstrate the actinomycosis fungus made the over-looking of any pyococci, which might have been present, impossible.

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Mycetoma, Madura foot.

An affection of the feet and hands, endemic in India, in which they swell up and are penetrated in all directions by canals and fistulæ. These communicate with one another, have smooth walls, and end on the surface in elevated or funnel-shaped, fistulous openings, from which exudes a fluid mixed with small bodies. According to their colour, a black and a yellow variety are distinguished.

Carter, to whom we owe the first description of the disease, regarded the yellow variety as a degeneration of the black, and cultivated from it a red fungus, the "Chionyphe." Later, he suggested the view that this was the cause of the disease, and drew attention to its resemblance to actinomycosis, which had just been discovered. Kanthack, who has recently thoroughly investigated the histological relations of this affection, has established the relationship of the two diseases.

On section of a madura foot there appear many large and small spaces, which are connected by canals, and seem to be excavated in the skin and hypoderm. The tarsal bones are softened and likewise beset with cavities, as are sometimes also the metatarsal bones. In the black variety these spaces contain a hard and dark, in the yellow, a soft, ochrey, fatty or gelatinous substance.

The tissue changes, which are produced in the skin by the growth of the fungus, Kanthack describes thus: the first re-action consists in a collection of round cells around the fungus—stage of simple inflammation and of fresh growth of the fungus. Then there is formed around it a granulation tissue with epithelioid cells and many vessels, while the fungus shows appearances of degeneration, which, as in actinomyces, are indicated by the formation of a hyalin rosette. At the same time there is found in the tissue around, a scattered formation of pigment. The third stage consists in the transformation of the granulation tissue into fibrous tissue, and the formation of abscesses and fistulæ around individual collections of the fungus, which may run together or rupture externally. Each of these spaces then shows, outside, a fibrous, often pigmented ring, then granulation tissue passing into a zone of leucocytes, and finally, immediately around the fungus, granular debris. The fungus then shows complete development of the

rosette, or further changes; the greatest degeneration is found where the fungus is closely encapsuled by fibrous tissue.

As a whole the fungus has, in common with actinomyces, the peculiarity that it extends directly in the tissue, without relation to blood or lymph vessels, forms definite canals, and does not metastatise. But even in its finer histological characters it is remarkably like it; it forms packets as large as a lentil or a pea—somewhat larger than actinomyces — which are round or mulberry-shaped. The larger, mulberry-formed packets break up on pressure into the elementary forms, which consist of a mycelial tangle, on which, outwardly, a crown of very small, plump or elongated hyalin clubs is radially arranged. The rosette is—as in actinomycosis—not completely concentric, but eccentric, half-moon-shaped, and on the concave side presents a hole from which the mycelium extends perpendicularly. The mycelial threads are finer than in actinomyces, loosely tangled in the centre, and they form, outwards, a marginal zone, from which fine mycelial threads extend in a brush-like fashion, and partly pass into the hyalin clubs, which, closely pressed together, form the rosette. When the granulation tissue around the fungus is fully developed, the rosette degenerates into the glassy, greenish, homogeneous border, while the mycelium is converted into a blackish mass; at the same time there appear masses of brown or black pigment, irregularly distributed in the central and marginal parts. In other cases the pigment forms a sheath round the mycelial threads, which do not then stain. Kanthack also describes other forms of degeneration, in which the bodies show black masses with cog-wheeled outlines. As a whole, the author favours the view, that the black variety is a degeneration of the normal yellow Mycetoma, for he could determine histological transitions, as Lewis and Cunningham did a clinical relation between the two forms.

Kanthack further notes the presence of Russell's "fuchsin bodies" in the granulation tissue, which probably represent the same change as the hyalin degenerated connective tissue cells, which, though not in such quantity as in actinomycosis, I found in all sections of mycetoma.

By the kindness of Dr Kanthack I obtained a piece of mycetoma, which he described as representing the third stage of the disease. It consists of firm fibrous tissue, which is permeated by pretty wide canals filled with fungi, and only shows at its border a remnant of granulation tissue. From the examination of this piece I can only confirm Dr Kanthack's statement, that the mycetoma fungus very closely resembles actinomyces. On the other hand, there cannot be a moment's doubt, that a whole series of important distinctions

separate the two fungi, and that there is no question of their identity.

As to the differences of the surrounding tissue, and its changes in the two diseases, which are evidently present, I can say no more, for my specimens of actinomycosis presents an earlier stage than those of mycetoma: I will only note, that the more chronic and benign course of the latter disease permits the development of a firm, dense change of the cutis and subcutis, which is very rare in actinomycosis.

The histological differences in the arrangement of the fungi in the two cases are however striking enough. While the actinomyces only produces round bodies, in mycetoma these only form the initial stage. In my case I found them only in small, lateral, evidently recent buds of the fungus. The main body consisted of a transparent, colloid mass, which showed no formation from clubs, and inside which the central hyphæ were arranged in peculiar windings. By appropriate staining, to which I shall immediately refer, these homogeneous masses, which compose the main part of the fungus body, may be analysed into closely arranged clubs, which are seated in a festooned form all round the fungus mass. But these clubs are incomparably larger than the familiar small clubs or rays of the actinomyces; they do not possess the finger and toe form of the latter, but extend conically, streaming out like the ribs of a fan, and are partly united. In their demand for space they depress the original globular middle part, and that consequently developes the looped windings already referred to, and is rolled out to an irregular twisted surface. Outwards, the much enlarged clubs press on each other, and are then indented in many places, get a wavy outline and partly run together into a net-like seam. There thus appear, with good staining, between the masses of fungi, peculiar, arabesque figures like fan palms, which are quite foreign to actinomycosis.

Like the forms, the staining relations of the two fungi are fundamentally different. While the rays of actinomyces stain brilliantly with acid fuchsin (if it is first fixed by anilin-xylol and then decolorised with anilin), in mycetoma only the younger clubs are stained by this method, and much more faintly, while the colloid, fan-shaped clubs are not stained at all. The demonstration of their structure is a very difficult matter; with the ordinary basic and acid colours, it is quite impossible. Only very powerful staining with hæmatoxylin gives a suggestion of it. I have only succeeded in successfully staining these structures in the following manner:—powerful staining with saffranin, contrast staining in water-blue and decolorisation in alcoholic (neutral or acid) eosin. The latter stain is itself not visible, it only serves to differentiate the *water-blue*, which has the nearest

relationship to the large colloid clubs. On the other hand, the hyphæ of the mycetoma are very easily stained. Like the actinomyces filaments, they stain well with all the iodine methods, and in addition, with very many of the most varied colours (even with carmine), by which the actinomyces' filaments are not stained. Like Kanthack, I got the best results with hæmatoxylin. Although the actinomyces filaments take up hæmatoxylin quite well, the staining in mycetoma is much more powerful, and a contrast stain is more persistent. If then one stains a section, which contains one of the fungi, with acid fuchsin and then with hæmatoxylin, fixes with anilin-xylol and decolorises in anilin, one can establish the diagnosis, even with a low power. The actinomyces are coloured brilliant red with just a suggestion of a central blue part; mycetoma shows bluish black-stained masses, embedded in a homogeneous, unstained substance, and only here and there surrounded by reddish clumps and fragments of clubs.

The substance of the glassy surroundings of mycetoma is therefore not the same as that of the clubs in actinomycosis. The latter may be called hyalin, for on sections they show exactly the same colour as the hyalin clubs of the surrounding granulation tissue. But in corresponding sections of mycetoma, the hyalin products of the connective tissue stain as usual, the glassy surroundings of the fungus not at all.

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Oriental boil, Dehli boil, Oriental ulcer.

A painless, chronic skin affection, frequently endemic in hot countries, which appears singly or on several parts of the body, in the form of firm nodules, chiefly on the exposed parts, such as the cheek, nose, eyelids, hands and legs. It begins as a small nodule like the bite of an insect, which may grow to the size of a shilling or even of a crown, is sharply defined from the healthy surroundings, over which it is very little or not at all elevated, and is livid red, at first smooth, but later scaly. In the centre there appears a softening, the moisture which exudes forms a crust, which extends in segments, something like an oyster-shell, and covers the whole nodule. Underneath there is a superficial loss of substance with irregular borders, which heals slowly under the scab, usually in the course of a year. It affects mostly young people and children, though not under one year old, especially in the autumn, at a time when many insects are about. The

nodule is auto-inoculable, and as the experiments of Weber, Villemin, Boinet and Deperet, Hickmann, Laveran and Heydenreich show, is directly communicable from man to man.

The finer histology of this most interesting localised infectious disease must be studied locally, with quantities of material, to settle many questionable points. Our present knowledge comes from some cases which have reached Europe, which were examined by Riehl and Leloir. I can control and add to their statements from a portion of a boil which Professor v. Düring kindly sent me from Constantinople.

Riehl found, in the epithelium, the horny layer loosened, the prickle layer at the periphery multiplied, towards the centre thinned, and in the centre itself altogether gone, so that here the infiltrated cutis directly adjoined the scale. At the thinned parts the prickle layer stained feebly. The distinct infiltration of the cutis passed, at the periphery of the nodule, into individual foci and processes, which followed the vessels, had no connection with hairs and glands, but possibly also extended along the lymph vessels. The collagenous fibres, which were separated by the cellular infiltration, showed a vitreous swelling, and were difficult to recognise in the centre. The cells were partly degenerated, more faintly stained and cloudy, and formed epithelioid and giant cells. Between them were found hyalin spheres and rounded masses, not unlike rhinoscleroma balls. Leucocytes were sparingly present in them. In the centre Riehl observed a small necrotic band, ascending vertically from the subcutaneous tissue to the epidermis. In the centre of the nodule the follicles had disappeared, but the coils and glands were seen embedded in the infiltration. The blood vessels showed growth of the epithelium, even to obliteration, hyalin degeneration, and still further out thickening of the media. By staining with concentrated gentian-violet solution, and careful decolorisation in 1% acetic acid, Riehl was able to recognise in cells, usually in the cloudy cells in the centre, more rarely in the leucocytes, cocci with a distinct membrane, and a diameter of 0·9 to 1·1μ, and as many as twenty in one cell.

Leloir found the same condition, a diffuse cellular infiltration, considerable in the centre of the nodules, passing at the periphery into individual islands, which surrounded the vessels and the coil glands, and reached into the hypoderm. Giant cells, Leloir found only very sparingly, and he was unable to find the hyalin bodies and masses described by Riehl. He found the hair follicles, and occasionally the coil glands, in the centre of the nodule, destroyed. He recognised also an endarteritis obliterans, and further, the preservation of the nerves. In the epithelium he found, in addition to the irregular growth and

the thinning in the centre, vesicle and pustule formation, which are also described clinically, as varieties of the boil. In spite of diligent search he could only find, in one section, one diplococcus, free, between the infiltration cells.

Poncet de Cluny found, with the iodine method, cocci in large zoogloœa masses, and a bacterium measuring 0·5 to 1·5μ.

Duclaux and Heydenreich and Chantemesse cultivated from the juice and the tissue of the oriental boil and the blood of the patient, what was probably the same diplococcus, measuring 0·2 to 1μ, which was also present in zoogloœa, and possibly corresponded with the cocci found in sections.

But no distinct successful inoculation with a pure culture of the micro-organism has as yet been made.

In my specimen, which came from the orbital region, there is likewise cellular infiltration, reaching from the epidermis deep into the hypoderm, and, as Riehl and Leloir state, numerous small, dense foci around the vessels. The cells are small, granular, mostly round in form and easily distinguished from leucocytes, for the blood vessels running through them are wide, contain many leucocytes, and permit the escape of many into the surrounding lymph spaces. The cells are, however, poor in protoplasm, and only at the periphery was I able to find a few plasma cells. The lymph vessels, and still more the lymph spaces, are, all through the preparation, unusually wide, leading to marked œdema, and thus the absence of plasma cells is not remarkable. This has a certain resemblance to the cellular infiltration in Ulerythema centrifugum. I found the surroundings of the coil glands strikingly free from infiltration; they are embedded in œdematous connective tissue, and their epithelium is large and clear, evidently swollen; in their lumina are found free fragments of protoplasm. The hair follicles also are beset with serous exudation and a remarkable number of leucocytes with elongated nuclei. Many of the eyelashes, which run through the nodule, are falling out, softened; the prickle layer of the hair follicle is folded and separated by wide spaces, showing here and there epithelial abscesses. The same changes are seen in the œdematous prickle layer of the surface. Further, there is found in the hair follicles a considerable number of mitoses, which are no doubt to replace the hair. In the centre of the cellularly infiltrated connective tissue there are enclosed necrotic areas, in which the collagenous bundles are very badly stained, the cell bodies no longer to be recognised, and the nuclei broken up. If the section is stained for fibrin these parts show a quantity of it. Fibrin is present elsewhere in the tissue, both in the collagen, and in the œdematous epithelium; I even found a duct filled with granular fibrin.

I was no more fortunate than Leloir in finding bacteria, especially Duclaux's cocci. Nor with Riehl's method (gentian violet, acetic acid) did my sections show any cells filled with cocci; but the mast cells—though there were not many of them—were naturally very prominent.

I could find no hyalin metamorphosis of the connective tissue cells, as in rhinoscleroma, and the collagenous fibres showed no distinct hyalin reaction.

From my observations I must then regard the process as a chronic sero-fibrinous inflammation of the whole cutis, which leads in the centre to necrosis, softening and consequent ulceration, just as in certain tuberous tertiary syphilides. The endarteritis, which I also found in many of the subcutaneous vessels, is certainly not the origin of the necrosis; even were it more extensive and greater than it is, it would not, according to my experience, produce any necrosis of the skin. The infection and the persistent exudation sufficiently explain the small circumscribed areas of necrosis. The absence of a formation of plasmoma and fibrous new growth corresponds to the clinical absence of an actual tumour formation and hardness. The greater saturation and fibrinous permeation of the nodule in my case correspond more to Leloir's case; Riehl had evidently examined a drier and harder node (from the ankle).

In conclusion, I must not forget to note that in a section of Riehl's case which he kindly sent me, the masses of cocci were distinctly seen. When the section was stained again with the iodine method, they appeared in enormous numbers inside the necrotic cell masses, but all of them were, so far as I could see, inter-cellular.

As this very deficient examination teaches, and the double name oriental boil and oriental ulcer indicates, the affection stands on the borders of our third and fourth groups, since it shows a tendency both to necrosis and to the formation of tumours. I have therefore placed it at the end of the third group, making its definite position dependent on future better knowledge.

The Pendjeh ulcer, which is no doubt closely related to oriental boil, I have not had the opportunity of examining.

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(d). *Inflammations with tendency to tumour formation.*

(a). Remaining local.

Erythema bullosum vegetans.

This affection, first described by Neumann, and unfortunately named Pemphigus vegetans, is a local infectious, auto-inoculable dermatosis, which affects especially the genital regions, axillary cavities, the lips, and mucous membrane of the mouth, and, especially at the contact surfaces, leads to characteristic growths, like syphilitic condylomata. After inoculation on healthy skin, there appears first a red spot, the size of a threepenny bit to a shilling, which may extend in one or two days to the size of the palm of the hand ; it has sharply-margined erysipelas-like borders, and there appear in the centre, large, thin-walled blebs, which soon dry up spontaneously into crusts. Then the base of the bleb is elevated into warty tumours, which, at the contact surfaces, become moist and condylomatous, and may reach the height of a centimetre, and extend peripherally beyond the region of the primary erythema, which for a time they margin. Later, the growths extend, usually preceded by a reddened vesicular wall, and finally cover the greater part of the body, if sepsis or marasmus does not lead to death. This is usually caused by eruptions in the mouth of an ulcerative aphthous type, which prevent proper nutrition. Most cases end fatally in three or four months. After excluding all cases of syphilis vegetans and the cases of pemphigus with sporadic growth of the base of the vesicle, there remain only very few cases ; up to now (1892) about twelve (compare Müller).

In the first, erysipelato-bullous stage of the affection, the pemphigus-like stage, we have either blebs on a reddened ground, or scabs which have taken their place, or, finally, reparative growth over the eroded skin of young epithelium, leading to the second, condylomatous stage.

The pure bullous stage has not yet been examined histologically. My preparations only show crust formation. But this deficiency is not of great importance, for the conditions in the cutis, which at this stage are the most important, remain the same, and the nature of the bleb may be assumed from the crust which it produces. To the clinical erythema there corresponds a marked dilatation of the superficial blood vessels and an œdema of the uppermost layer of the cutis, which consists of the flattened out papillary body. Directly under the flat adherent crust, the dilatation and turgescence of the blood capillaries is almost colossal; there is, in many parts of the sub-papillary net, stasis, but without any diapedesis of erythrocytes, except in the papillary loops, from which many small hæmorrhages have taken place. This corresponds to clinical experience, for the vesicles often have bloody contents. As is always the case in superficial stasis, not only do the contents of the vesicle, but also the whole remaining prickle layer, dry up into a horny, nucleated, very deeply-stained layer,

which behaves and stains like dried up pus. Consequently the crust reaches everywhere down to the connective tissue margin, and the repair of the epithelium must take place from the unaffected borders or the glandular or follicular epithelium. The resemblance of the dried epidermis to pus is only external, caused by the very great quantity of nuclear inclusions. The absence of leucocytes in the superficial layers of the cutis and the over-lying horny layer shows that we have to do with nuclear fragments of the epithelium. It is then a pure epithelial necrosis, produced by stasis.

The dilatation of the blood vessels diminishes towards the subcutaneous vascular net, and, as a whole, the cutis is little altered. The spindle cells are somewhat enlarged; the collagenous and elastic tissue is still well preserved. Only the coil glands show, in some of their loops, œdema of the epithelium and dilatation of the lumen, which is filled with a coagulated mass. Sometimes the cellular œdema of the coil epithelium is so great as to obliterate the epithelial borders. The epithelium of the ducts does not share in this change.

In the stages of transition to the condylomatous stage, the epithelium from the sides, and from the ducts and follicles, pushes itself under the necrotic epidermis, and sends a vigorous ridge net into the cutis, producing a new papillary furrowing. The crust then consists in its upper layer of old horny layer and dried up vesicular contents; in its under, of dried, and therefore necrotic prickle layer.

To conclude from these observations in the crusted period, we may expect, in the vesicle, a simple serous elevation of the horny layer, with or without elevation of the most superficial layers of the prickle layer, but neither a purulent nor a colliquative formation of vesicles, due to breaking down of the prickle layer. The commencement of the affection is a paralysis of the blood vessels, going on to stasis, with subsequent swelling of the upper layers of the cutis, elevation of the horny layer, and simple epithelial necrosis.

The transition stage is little characteristic, only the œdema of the coil epithelium and the swelling and multiplication of the perithelium, as well as a persistent dilatation of the blood vessels, recall the changes of the first stage, while the new epithelial proliferation points to the later ones. It almost appears as if the *status quo* had again been attained. But new histological changes are already in preparation, leading to most characteristic appearances, which are pathognomonic of the affection. These concern the surface epithelium and the prickle layer of the hair follicles, then the coil glands and their surroundings, and, finally, the whole circulatory system of the skin.

The over-growth of the erosions, caused by the vesicular elevation, does not remain normal, but constantly extends, and leads to grotesque

thickenings of the epithelial ridge system, which resemble the most luxuriant growths on a syphilitic basis and in acuminate condylomata. The papillæ are mostly only passively elongated and divided, but in some places, especially at the under end of the epithelial ridges and processes, the connective tissue grows actively into the prickle layer. These places are indicated by the rapid new formation of cells in the small papillæ, the resemblance of the latter to the papillæ of sprouting hairs, and the regular pallisade form of the basal prickle cells. Thus the surface of the papillary body becomes more and more varied, and its result on the surface epithelium is to cause it to show a quite irregular, twisted arrangement, spiral processes crossing and winding, as in certain carcinomata.

To this severe, irregular acanthosis is added, as a second characteristic phenomenon, immigration of leucocytes into the epithelium, without much serous and fibrinous admixture. It is, in general, striking, that the inter-spinal lymph spaces are by no means particularly dilated, although the lymph tracks of the papillary body, as we shall immediately see, show a very marked distention. The wandering cells simply collect in large quantities at certain points of the prickle layer of the surface, and mechanically separate the epithelial cells. These "dry abscesses" of the prickle layer strikingly contrast with large, purely serous spaces in the epithelium, which form in connection with the dilated lymphatics of the papillary body, and form the third characteristic feature of the epithelial change. In many places the thin wall of the widely dilated superficial lymph spaces is lost, so that the bases of the epithelial taps are directly washed by the cutaneous lymph. Instead of the dilatation of the cutaneous lymph spaces becoming continuous with that of the epithelium, as in many other dermatoses (*e.g.*, Ulerythema centrifugum), that is exactly what does not happen. Instead of it, single epithelial cells and larger collections of them break off, and lie loose in the large lymph spaces at the surface of the cutis. And further, the cutaneous œdema penetrates here and there between the basal cells, and leads, immediately over them, to large, monolocular, serous cavities, inside the prickle layer of the surface and of the hair follicles, without the surrounding lymph spaces of the epithelium being dilated.

Both the "dry abscesses" and the serous cavities indicate the resistance of the proliferated prickle layer to the powerful lymph stream of the cutis, as does the absence of general dilatation of the lymph spaces and colliquation of the epithelium. It is the same resistance of the epithelium which shows itself clinically in the durability of the condylomatous growth and the inefficiency of external remedies. This it is also which mainly distinguishes the epithelial

growth here present from the similar one in acuminate condylomata and syphilis.

Not less remarkable are the alterations in the coil glands, which were œdematous, even in the early stage of the affection. The œdema of the epithelium constantly increases in the loops of the glands, until the marginal epithelium is a clear, unstained mass, while, at the same time, the internal layer of epithelium proliferates at many places and fills the lumen with young epithelium. The ducts, which are at first normal, are dilated into twisted, constricted cystic cavities, though not everywhere to the same extent. It seems to me that the difference depends on the fact, that in some sweat pores there are, in relation to the proliferating prickle layer, collections of leucocytes, practically white thrombi, which favour the cystic degeneration of the ducts. The loose connective tissue, surrounding the gland as a whole, is very much swollen and gelatinous, so that the glands appear to be embedded in an almost homogeneous substance, sharply marked off from the rest of the cutis.

In the cutis we have first to consider the cellular infiltration. This is very different in different preparations, and therefore is by no means characteristic. Where it forms continuous cell masses, it is always limited to the upper layers of the cutis, and only sends processes along the vessels, both into the subcutaneous tissue and into the larger papillæ. Only occasionally, and only in the centre of the densest infiltration, are any plasma cells formed. Evidently the great œdema of the cutis is not favourable to their development. Most cells show the type of ordinary spindle cells, a few that of small, atrophic plasma cells. C. Müller, to whom we owe most of the foregoing, has finally drawn attention to important changes in the blood and lymphatic vessels. There is a very striking incongruity between those of the cutis and those of the hypoderm. The former, especially the veins, show a maximal, almost angiomatous dilatation and twisting, extending into the papillary body. The lymph vessels also are here very markedly dilated, and pass at the epithelial margin into the pools of lymph above described. The system of lymph spaces is also dilated, the structure of the collagenous tissue is loosened, although only in the papillæ, and—as noted above—in the neighbourhood of the coils, softened and clear, swollen and gelatinous. The elastic tissue of the cutis and of the papillary body has largely disappeared; only fragments of it are seen between collections of cells.

The common character of these changes in the papillary body and the cutis is one of serous inflammation and of great venous and lymphatic stagnation. In the hypoderm this character is only marked around the coils, which are found in the subcutis as isolated œdema-

tous areas. Otherwise the collagenous and elastic tissue there is normal, the number of cells only moderately increased, and, a very important point, the blood vessels are actually narrowed by obliterative inflammation. We can distinguish an endo-, meso-, and peri-arteritis and phlebitis. The narrowing of the lumen takes place usually by flat concentric layers of connective tissue, but is often unilateral and partial. It is evidently to be regarded as a regulatory phenomenon to avoid the stagnation of blood, and consequently of lymph on the surface of the skin. Possibly there is, in the endophlebitis obliterans which developes, an excessive protection of the circulation, which favours the lymph stagnation at the surface, and possibly explains the striking obstinacy of the epithelial growths.

Finally, it must be noted, that the thick epithelial layer of the surface, though only covered by a relatively thin horny layer, very rarely shows erosions and degenerations. In spite of the softening of the upper horny layer into a slimy covering, and in spite of persistent external treatment, we find only very rarely, considerable necrosis or the opening of one of those epithelial abscesses, with breaking down of the epithelium over it.

The hairs and sebaceous glands which are accidentally present, play a purely passive part. The latter appear gradually to atrophy. I have already noted that dry abscesses and the lymph pools may also be present in the prickle layer of the follicle.

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Rhinoscleroma.

An infectious tumour, limited to the nasopharyngeal mucous membrane and the adjacent skin of the nose and upper lip, which leads to blocking of the nasal cavities, and widening and cartilagenous hardness of the nose. The surface of the skin is smooth, shiny, usually brownish and marked with dilated veins, contains no hairs or glands, and at the angle of the nose tends to crack. It grows as a hard nodule on the inner side of the ala nasi, on the septum, or on the upper lip, is brownish red in colour, grows very slowly but steadily; it is entirely painless and shows absolutely no tendency to spontaneous breaking down. The skin around the tumour is always perfectly healthy, there is no swelling of the glands and no affection of the general system. v. Frisch first demonstrated in the tumour a capsule bacillus, which by its constant presence in all later investigated cases has been recognised as the cause of the disease. The inoculation of pure cultures on animals has not been successful (Mibelli, Dittrich).

Thanks to a whole series of recent able works, the individual histological changes and the relation of the bacilli to the cutaneous tissue in this disease have been closely studied, and yet it is more difficult than usual to give a summary description of the structure of the diseased skin. There is no regular sequence, no uniform starting-point of the change, unless it be in the lymphatic vessels. This general irregular formation depends on the great chronicity of the condition; changes are everywhere visible, but can never be followed to a conclusion. According to the place from which the piece was excised, the appearances differ, and only the elementary lesions are found everywhere the same. These we will first consider by themselves.

The basis of the tumour is composed of large, typical plasma cells, which are present in such quantity, that we may take rhinoscleroma as the type of a plasmoma. They usually lie in large collections, irregularly scattered in all the layers of the skin, both under the epidermis and in the subcutaneous tissue, they accompany the blood vessels in the younger parts, which, towards the margin next the healthy surroundings, consist mainly of equally well-formed plasma cells. At these places the collagenous tissue is always reduced to a net-work of fine fibres, and the elastic tissue has disappeared.

But we see few spindle cells, particularly none of the large, swollen forms, and no spider cells, as in most other plasmomatic tumours. Most of them lie in the neighbourhood of the collagenous bundles, which stretch into the plasmoma, usually close to them. With them, there are always enclosed in these collagenous bundles, a few compressed and elongated plasma cells.

The collagenous tissue is only exceptionally normal; while in the plasmomatic areas it appears rarefied, it is thickened and increased at most parts of the tumour, and, as usual, at the expense of the spindle cells. The plasma cells certainly do not directly contribute to the hypertrophy of the collagenous tissue, but it appears possible that inside the fibrillary bundles some of them are re-transformed into spindle cells, and thus give origin to new fibrillary tissue. The distribution of the hypertrophic collagenous tissue is as irregular as that of the plasmoma; it is found, close under the epidermis, as in the subcutaneous tissue, mostly in the form of coarse processes and bundles, running parallel to the surface of the skin. It streams into the already formed plasmoma, which it replaces, after it, in turn, has displaced the normal connective subtance.

This collagenous hypertrophy, like the fibroma of syphilitic and tubercular tumours, is clinically of great importance, for on it depends the pathognomonic hardness of rhinoscleroma. It is owing to the

superficial and widespread position of the fibrous processes that we do not have soft plasmoma nodules embedded in hard fibromatous tissue, as in tertiary syphilis and in the sclerotic forms of lupus. We have, close together, plasmomatic and fibrous parts, and the latter alone causing the flat and hard tumour, for the plasmoma never—as in lupus and gumma—leads to swelling, spherical areas, completely free from collagen, and further, the masses of small plasma cells (daughter plasma cells) are not present in rhinoscleroma. Mast cells are present in moderate but not striking amount.

As the tumour developes the hair follicles atrophy, as do partly the coil glands, without showing any signs of inflammatory proliferation. The surface epithelium, on the contrary, is here and there thickened, but the a-typical growths show no similarity and nothing characteristic of rhinoscleroma. In the more prominent parts of the tumour the epidermis is, on the contrary, usually flattened and thinned.

Together with these progressive changes, we have regressive ones, more characteristic of rhinoscleroma. There are two distinct regressive metamorphoses of the plasma cells. Mikulicz first demonstrated markedly dropsical, Pellizzari hyalin degenerated cells. These two degenerations were confirmed, and sometimes confounded, by later authors; they were first distinctly separated and thoroughly described by Mibelli.

In the dropsical cells, v. Frisch found bacilli, to which he ascribed the degeneration. According to this author they develope from round cells, and increase in size and degeneration with successive additions of bacilli. Then Mibelli showed that, at certain parts of the rhinoscleroma, at first the cartilage and the softer parts of the tumour, which tend to block the nasal openings, these usually single cells are present in greater numbers, and the rhinoscleroma tissue, usually so hard, has a peculiar gelatinous softness. The very large dropsical cells then lie closely together, only penetrated by fine collagenous fibres, wide lymph spaces, and blood vessels. They have a definite contour, a large meshed spongioplasm, in which is a very faintly refractile, almost unstained, evidently semi-solid mass, and a diminished facetted nucleus. Around these altered cell masses there are exceptionally seen transitional cells, which, except for a slight diminution, show unaltered protoplasm and a normal nucleus. But it is still evident that they are degenerated plasma cells. They develope from them, the deeply granular protoplasm first disappearing from some meshes of the spongioplasm, and then from the whole cell. At this stage one can often recognise six or eight bacilli in the cell, near the nucleus, which are always pretty regularly arranged. But this stage appears to be

a short one, for almost all the dropsical, reticulated cells are equally large, have wide meshes, and very often spaces, filled with fluid, which have developed from the confluence of the elementary cavities.

Mibelli has put forward the view, that the semi-solid substance in the cell consists of liquefied bacillary mucus, which gradually compresses the protoplasm and distends the spongioplasm of the cell to these dimensions. This view would gain much in probability, if it could be proved that all the large dropsical cells were filled with bacilli, for with the ordinary methods of staining this is certainly not evident. But Mibelli's new method of staining the bacilli with alum carmine shows the dropsical cells so frequently occupied by bacilli, that I venture to adopt his view for some of the cells. It is remarkable, that even the largest cells, which are quite filled with bacilli, still show a sharp, uniform, well-stained, oval contour, which the so-called "lepra cells" do not possess. Where this cell membrane bursts, the fluid contents and a number of the bacilli escape and fill the nearest lymph spaces, some of the bacilli usually remaining adherent to the fragments of the membrane.

The hyalin cells are usually isolated, more rarely in small collections, never in such numbers as the dropsical. They have been carefully studied by Pellizzari and by Cornil and Alvarez, v. Frisch, Wolkowitsch, Mibelli, and Noyes. Noyes had the opportunity of examining the transitional stage of the infiltration cells into the hyalin clumps, and he described them as swollen, granulated cells, staining deeply with eosin. These cells lose their granular appearance, become homogeneous, and take a fainter eosin stain; the breaking down into small spheres or facetted portions may commence at any stage of the swelling. The nucleus is often retained to the end, and the fragments or small hyalin spheres escape from the distinctly nucleated membrane, form at first a common collection of spheres, and then gradually distribute themselves with the tissue juice in the lymph spaces. Most of the hyalin cells have, like the dropsical, a diameter four or five times that of the surrounding plasma cells, corresponding to the extensibility of their membrane; but they are almost always spherical, never oval like the dropsical cells, on which the tissue pressure has more effect. Mibelli suggests that the contents of these cells also are a modified glœa of the bacilli. He found, in some hyalin cells, a breaking up of the mass into rods (like cigar bundles), and he derives the spheres from single, the rods from chain-formed or connected bacilli, whose external mucous mantle has undergone a colloid change. In view of the importance of this question in relation to hyalin connective tissue cells in general, which, even if only singly, are found in almost all infectious processes of the skin, I asked Dr Noyes to test this view by

staining, and as a matter of fact, he found in some of the colloid spheres and fragments a central point or streak, taking a different stain, and resembling an enclosed bacillus.

Some recent investigations of my own with modified staining methods, have made me once more very doubtful of the bacillary nature of these bodies.* If the hyalin masses are treated with alum solution of gentian violet and iodine, and then with orange in a mixture of anilin and xylol, a number of the hyalin spheres retain the blue colour (iodophilic), while the majority take the yellow colour of the orange (acidophilic). This is not a mere matter of chance, one can determine that only the latter are in the transition stage, described by Noyes. The transformation in the orange-stained hyalin cells takes place thus: the body of the plasma cells increases, usually at one side, while by taking up the acid orange colour they are distinguished from the other plasma cells. At this stage the cells appear pretty homogeneous, but whether the basophilic granulation has disappeared it is not possible to determine by this method. The more these orange-stained cells enlarge, the more apparently granular they again become, although now they are larger, round, shining, irregular bodies which, in great numbers, closely fill the whole cell body. Finally, the cell bursts, and its contents escape in the form of a debris of coarse, round, shining granules.

From these cells, with numerous small hyalin bodies, I see no transition to the iodophilic cells with smaller, blue, hyalin spheres. These latter cells show none of the transition stages described, but, inside a faintly acidophilic protoplasm, a greater or lesser number of equal or irregular hyalin spheres, which, in contrast to the rest of the protoplasm, take the blue colour, first faintly, as they become older, more powerfully. While the hyalin spheres continue to grow the cell membrane is distended, and if it will yield no further the hyalin spheres are flattened and become facetted. They do not appear to run together.

If the preparations are treated for a long time with orange, the usually blue, hyalin spheres take, in their outer mantle, the yellow colour, and then show in the centre a bluish point or a rod-shaped nucleus. They evidently have a hard nucleus and a somewhat softer mantle. This, I think, explains the bacillary-like appearance of certain staining of the hyalin spheres (Noyes), better than an actual central bacillus, for the dimensions of the kernel are not constant, but may be

* After much research I recommend the following as the best general method for the simultaneous study of the bacilli and the hyalin degeneration in rhinoscleroma: deep staining in picro-cochineal, gentian violet with the addition of concentrated solution of alum, iodine treatment ($KaI + H_2O_2$), and decolorisation in a mixture of anilin and xylol with a little orange.

influenced at will by the staining. The rod or finger-shaped hyalin forms, in some cells, always show the blue colour.

There are then among the hyalin cells notable differences, which at least indicate a different density, and perhaps chemical differences in the hyalin; at least I have never succeeded, with any method, in recognising with certainty a rhinoscleroma bacillus inside the hyalin cells. And further, I have learned from other pathological experience, that a very widespread hyalin degeneration of connective tissue cells may appear in the neighbourhood of organisms, whose character completely excludes their penetration into degenerated cells (c. *Actinomycosis*).

While, therefore, the hyalin degeneration of the cells must be regarded as a distant action of the bacilli, very characteristic of rhinoscleroma, the dropsical degeneration of the cells is, *at least partly*, due to the penetration of the bacilli into the cells themselves. I admit that such a partial concession is very unsatisfactory. While there is no doubt that in some cases the reticular dropsical degeneration may take place without penetration of the bacilli, it is not actually proved in any individual case that it is induced *by* the bacillary invasion. But it is possible that better staining will show organisms in those dropsical cells which we now regard as empty, and also that the faintly staining substance in the meshes of the dropsical cells has arisen from the liquefaction of the bacilli and their capsules. In this connection I would point out to future investigators, that, in certain variations of the pararosanilin iodine method, all dropsical cells without exception are filled by different-sized, round, blue granules, which are certainly not bacilli, though they may be their degeneration products.

The rhinoscleroma bacilli mostly lie, as well as inside the dropsical cells,—this Alvarez has made quite clear—embedded in glœa, free in the lymph spaces and vessels. The glœa, like the mucus of lepra bacilli, is readily browned by osmic acid, and is thus best demonstrated; this treatment further renders it more easily stained. The bacilli lie in it, often very regularly distributed at considerable intervals, which indicates a considerable production of mucus. In many preparations, especially those which are taken from the periphery of the affection, all the bacilli lie in the lymph spaces, and there are no dropsical cells, but a considerable number of hyalin ones, which are, in general, much more equally distributed through the whole tumour. The lymph vessels and spaces filled with bacilli then extend, not only between the areas of plasma cells, but also far into the fibromatous processes. Here there may be no cells to cause confusion, there can be no doubt of the free position of the bacilli, and its assumption in the dropsical parts of the tissue is therefore justified. From this condition at the

peripheral parts of the tumour, we must assume that the original and main spread of the bacilli takes place in the lymph tracks filled with mucus; and only at a certain stage of the affection, especially deep down, is that dropsical tissue formed, whose ceils also contain bacilli.

Then, of course, many (bacilli-containing) lymph vessels and spaces are dilated; but otherwise they show no abnormality. The blood vessels are mostly dilated, but very irregularly, they are almost always accompanied by plasma cells, which resist the degeneration described, longer than the other plasma cells. We have later, as in most granulomata, an obliterative inflammation in some arteries, which has the same significance as the fibromatosis of the whole tissue, and increases with the age of the process. Diapedesis of red blood corpuscles and leucocytes is not typical of rhinoscleroma.

We can now understand that, according as epithelial growth or thinning is present, according as plasmoma or fibroma, dropsical or hyalin degeneration predominates, and finally, according as the progressive and regressive processes have taken place more in the upper or lower regions of the tissue, are more adjacent or at some distance, sections of rhinoscleroma will appear very different. We can only say of the architecture of the whole tumour that, at the periphery towards the healthy tissue, the plasmoma, at a later date the fibroma, prevails, that the soft dropsical parts are especially found deep down at the cartilage, and that the hyalin cells are found in varying amount, but pretty generally throughout the tumour. Rhinoscleroma is always characterised by the peculiar multiform capsule bacillus, by the two widespread cell degenerations and the equally large, numerous plasma cells, which far exceed in amount all other connective tissue cells.

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Keloid of the neck.

Neck keloid is a tumour, consisting mainly of connective tissue, which developes from nodules arising round the follicles at the posterior margin of the scalp, and forms keloid, smooth, reddish or dark red, firm growths. There are depressions of the surface in the centre of the original hair circlets, from which extend brush-like stumps of hairs, and the tumour shows similar brush-like projections at its sharply marked edges ; otherwise the surface is hairless, shining, and not ulcerated. Morrant Baker, who first properly described the condition, regards the primary pustule not as ordinary acne, but as only acne-like, nevertheless he retained Bazin's name Acne keloid ; later investigators lay stress on the analogy with Sycosis (Besnier) and Keloid. That it is not a simple combination of true acne with keloid, is shown by the rare, quite different and well-known cases of keloid, developing in other parts of the body from true acne nodules ; the tumour would then certainly appear on the sternum, where both acne and keloid are frequently present, and not only at the back of the neck. It has as little to do with acne as with keloid, but is a peculiar, probably infectious folliculitis, localised in the neck, which leads to the development of a fibroma of keloid character. This method of development shows us that the affection should be reckoned with the folliculitides, or still better, with the tumour-forming inflammations of the cutis.

Roger found a pure connective tissue tumour, great dilatation of the vessels, but no small celled infiltration. The epidermis and the papillary body were intact, but all the glandular apparatus, except the few hair follicles, was atrophic.

Since then we have a series of observations from the French and Italian schools, all recognising an inflammatory commencement of the affection (Dubreuilh, Besnier, Vidal, and Leloir, Melle, Pellizzari, Mibelli), and their views only differ in so far as they regard either the sebaceous glands or the hair follicles as the point of origin, sometimes regarding the folliculitis and sometimes the secondary keloid as the main change. A specimen kindly sent to me by Prof. Audry, which in general confirms the results of the most recent, very careful work of Mibelli, enables me to make the positive statement, that in the folliculitis of keloid of the neck, neither the organisms of ordinary sycosis (staphylococci) nor of acne (acne bacillus) are present, clinically ; impetigenous pustules and true comedones are never found. The affection must consequently be regarded as a distinct one, and, until the infectious agent is better known, may from its pathognomonic seat be called Neck keloid, as Pellizzari has recently suggested. Histologically, as clinically, we distinguish two stages of the affection, that of folliculitis and that of keloid. The former is characterised by a perifollicular inflammation affecting the hair follicle in its whole extent, and certainly with no preference for the sebaceous glands. Mibelli found most of the perifollicular cellular infiltration, at the level of the sub-papillary vascular net and in the upper part of the cutis proper ; towards the

hypoderm it slowly diminished. The hair follicle and its prickle layer were beset with leucocytes, often, but not regularly, forming a small area of pus in the central part of the follicle. The upper part of the follicle epithelium may proliferate or remain normal. According to Mibelli, most of the inflammatory infiltration consists of lymph cells. In my preparations I find them to consist mostly of stationary connective tissue cells, both spindle and rounded ordinary cells, along with a few occasionally multi-nuclear plasma cells; leucocytosis plays here a very subordinate rôle. The hair itself undergoes no change, but the central part of the hair follicle frequently, and the sebaceous glands always perish from atrophy. Outside the hair follicles, the cellular infiltration accompanies the subpapillary and papillary vessels of the neighbourhood, and extends some distance downwards along the vessels. Mibelli also found giant cells around the hair follicles.

During this there has begun around the affected follicles that formation of fibrous tissue, which at the height of the process gives to it its peculiar character. At the more recent parts it consists of collagenous tissue, closely beset with large, protoplasmic spindle cells. The lines of the cutaneous tissue are retained, and we have therefore from the commencement a dense, irregular felting of bundles of coarse fibres, crossing each other in all directions. We have then to do, not with a collagenous tissue of a special nature, which only invades the skin in definite directions, such as along blood vessels, but with the transformation of the whole substance of the cutis into hypertrophic tissue. This tendency to the formation of fibro-blasts and new collagenous substance extends in all directions, especially from the under and middle parts of the follicles, diminishing towards the surface and beneath. The new formation of collagenous tissue is limited, as in true keloid, to the sub-papillary vascular net and the hypoderm, and so far as it reaches, the elastic substance completely disappears.

On the more recent parts the tumour looks exactly like a simple fibroma, or even a fibro-sarcoma. But on the older parts, where the protoplasmic fibro-blasts disappear more and more in favour of collagenous tissue, an interstitial growth of the existing bundles sets in. These are converted into broad, almost homogeneous fibres, the flat cell bodies are widely separated from one another, the lymph spaces between them disappear, and now first appears the great swelling and firmness of the whole tumour, which has earned for it the name of keloid.

For now, in consequence of the swelling, extending from certain points of the cutis, there appear, as in keloid, displacements of tissue. At first the adjacent collagenous bundles are arranged tangentially around the swollen centres and there develope rounded nodules of colla-

genous tissue, which project from the rest of the cutis, and by further swelling press the enclosed organs to a side. The cellular infiltration of the first stage gradually disappears, and gives way to a moderately cellular tissue, free from elastin, poor in vessels, consisting mainly of collagen. All the shorter and weaker follicles, as well as those in the bed-hair stage, atrophy, as do their corresponding sebaceous glands, and only those follicles are preserved which were originally deepest, *i.e.*, seated in the subcutaneous tissue, because the pressure of the fibroma on them is only lateral. Since these hair follicles all occupy the centre of the hair circlet, and represent the original inmates, one may say that the pressure of the tumour limits those hair circles, which it spares, to the innermost central follicles. These are further pushed together by the general pressure, and the hair follicle necks usually unite into a wide infundibulum. These form the externally visible depressions of the growth, into which a probe passes deeply, and from which a brush of hairs usually projects. At the outer periphery of the fibroma the hairs are obliquely laid, and now and again form a circlet of hairs.

But these great changes do not extend, as already noted, either to the hypoderm or to the coil glands, unless these are unusually high, or to the papillary body. The latter is, on the contrary, permeated by wide, over-filled vessels, is of loose, normal structure, indeed, may be in parts œdematous. Above the densest parts of the fibroma it usually contains a perivascular cellular infiltration, with a moderate number of plasma and mast cells.

We see, then, that this infectious fibroma is no more a proper Keloid than the initial folliculitis is a Sycosis or an Acne. From keloid it is distinguished by the diffuse irregular extension of the collagenous hypertrophy, and the processes are only similar in the secondary interstitial growth of the collagenous fibres and the consequent appearances of pressure, and in the arrangements of the parts.

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Elephantiasis nostras sive streptogenes.

By elephantiasis we unfortunately regard exclusively an *acquired*, *inflammatory fibromatosis* of *individual parts* of the body, especially of the legs and

genitals. There is a pandemic form, appearing sporadically in all climates, which developes after repeated attacks of streptogenous inflammation (erysipelas, phlegmon, lymphangitis) and a tropical, which is due to the presence of the Filaria sanguinis (elephantiasis filariosa).

The former, which we are here considering, is to be sharply separated from congenital connective tissue growths (elephantiasis congenita) and from circumscribed stagnatory fibromatosis. The latter is treated under fibroma. The fibromatosis, which should alone be described as *elephantiasis nostras*, is diffusely extended over one part of the body (extremities, genitals, face), is independent of any circumscribed stagnatory cause, but regularly developes in succession to erysipelas or a series of recurrent erysipelata. The latter are distinguished, even during healing, by the persistence of a doughy soft œdema, which indicates a persistent disturbance of circulation, brought about by the erysipelas. The soft consistence gradually gives place to a harder one, without the skin of the affected part returning to the normal. The underlying soft parts unite with the skin, which increases very much in thickness, and form a firm, immovable mass of tissue, which, in the course of years, may assume monstrous forms (elephantine foot, leonine countenance, &c.). It is characteristic of elephantiasis that the mass of tissue slowly but steadily increases, even when the rest of the body is emaciated by age or starvation. Additional extensive inflammation (eczema, ulcers) and stagnation (from garters, gravity) are not to be blamed for this steady increase, although they may favour the more rapid and greater development of elephantiasis. On the contrary every true erysipelas tends to leave the affected part more thickened. The development of elephantiasis by inoculation of erysipelas cultures was experimentally tested by Bockhart.

It is therefore in the highest degree probable that the true sporadic cases of elephantiasis develope from incompletely healed erysipelas—that is, those which leave behind disturbance of circulation, and are therefore in many cases not completely absorbed nor all the streptococci destroyed. According to this view, chronic persistent erysipelas and elephantiasis nostras are closely related conditions ; we know that one may pass into the other. But though the infectious cause gradually disappear, there remains a tendency to tissue hypertrophy. More interesting than hypertrophies and destructions under the skin, are the epithelial growths, which may lead, with more or less hyperkeratosis, to the most varied papillomatous, nævoid, ichthyotic structures.

In regard to the finer anatomy of Elephantiasis nostras we have a remarkable consensus of opinion among observers, in the explanation of the histogenesis, but a more or less apparent, complete incongruence of the same attempts at explanation. Most authors recognise in the lymph stasis, and the ectasis of the pre-existing lymph channels, a sufficient cause of the fibromatosis, and the origin of the whole process, firstly, without being able to prove a central obliteration of the lymphatics, which might explain the peripheral ectasis ; secondly, without giving any explanation, how a lymph stasis can account for progressive changes of the collagenous substance, which we are in general accustomed to look upon as the result of cellular proliferation.

And further, we have all the while the consciousness, that a central obliteration of the lymphatics (thrombosis, epithelial growth), even if it were constantly recognised, would, according to all experience of experimental pathology, lead to no such lymph stasis and lymphangiectasis, as is present in elephantiasis.

The old theoretical demonstration of the transition from central lymphatic obliteration to peripheral lymph stasis and consecutive fibromatosis rests then on two sophisms, *i.e.*, on an insufficient basis. Observers are even yet treading a weary circle in this connection, while the most fruitful basis of a clear demonstration of the pathogenesis has already been provided.

So far as concerns the extension of the lymph stasis, which is undoubtedly present, experimental histology teaches us, that this is only to be ascribed to a *resistance to the escape of blood.* We have, therefore, to seek the cause, not in the large lymphatics, but, if anywhere, in the veins of the skin. v. Winiwarter, who has much experience in this subject, writes as follows, and I cannot refrain from quoting him verbatim, although the author himself does not regard the facts as of value in explaining the lymph stasis :—" Most striking is the hypertrophy of the veins, which may become so great that the divided veins gape like arteries, while their walls, especially their adventitia, appear much thickened in concentric layers, and closely adherent to their surroundings ; their lumen is probably more frequently narrowed than widened, although, on account of the stiff walls, it looks larger than we are accustomed to see in divided veins. In an amputated elephantiasic leg I found the gaping subcutaneous veins at least as wide as the radial artery. These smaller branches felt just like the Vas deferens in the seminal cord ; at least thirty ligatures must have been applied to the upper third of the leg. The thickened veins are further *partly obliterated by a brownish, concentrically-arranged substance,* which runs through the intima and media, in the form of threads, to the thickened adventitia, outwards this mass is fibrous and firm, but in the centre, soft and spongy ; *other venous twigs contain thrombosed, brownish red coagula ;* the main branches are usually permeable, *only exceptionally degenerated into fibrous cords. The arteries are much more rarely affected than the veins.*"

Nothing more is required to explain a collosal lymph stasis and lymphangiectasis. Some of the veins show fresh thrombi, in others these are organised, in other words, an obliterative endophlebitis takes place and may even convert some of the branches into fibrous cords. The few persistent, completely permeable veins show an " eccentric hypertrophy," that is a compensatory hypertrophy of the muscularis adventitia, to compensate increased demands on them. Here we have

at once a classical, pathological, experimental basis for the explanation of all the lymph stasis and lymphangiectasis.

A number of older authors (Wise, Brett, Fabre, Bouillaud) had assumed a primary share of the blood vessels in the production of elephantiasic swellings, and Virchow, Birch-Hirschfeld, and Vanlair found the venous walls nodularly or diffusely thickened, and the adventitia abnormally cellular. Southam observed, in one case of marked elephantiasis of the leg, the larger veins dilated and gaping. Their adventitia was thickened, the media and intima were transformed into firm fibrous substance, arranged as in an aneurism. The outer layers were brown and firm, the inner, soft, spongy, and net-like. The same changes were found in the smaller veins, which resembled arteries filled with coagula, and were here and there obliterated, while the larger veins everywhere permitted the passage of the blood. Only the *saphenous vein* was transformed into a *thick fibrous cord*, and its opening into the femoral *was closed by an organised thrombus*. The arteries were narrow and their walls thin. Marcacci found, in addition to thickening of the walls and partial dilatation of the veins, numerous thromboses, the lymph vessels not dilated, the lymph glands atrophic. Although there exists then, on the one side, such a logical series of facts as make the first sophism untenable, we are by no means driven to the other side, as it might appear from previous demonstrations, to assume a direct dependence of the fibromatosis on the lymph stasis. As a fact, the histology of elephantiasic tissue supplies, as Rosa Welt first proved, sufficient proofs of another origin of the collagenous tissue, better harmonising with our other views on histogenesis, since we have already passed beyond the period of productive "blastemas" as well as that of the development of fibrous tissue from leucocytes (Young). This makes the second sophism untenable. Lymph stasis and fibromatosis are two processes which develope and advance quite independently of one another, although they may be combined. In most cases of elephantiasis nostras, the fibromatosis is the main element, while in elephantiasis filariosa (which see) the lymph stasis always plays a prominent and often a dominating rôle (lymph scrotum).

Elephantiasis developes from an œdema of the skin, which persists after the healing of erysipelas, and is to be ascribed to the persistence of gradually organising thrombi in the veins. It lasts long, until the hardness of the tissue has developed to a sclerodermatic process, and we must distinguish two periods of growth, soft and hard elephantiasis.

The first, soft period shows all the elements of the connective tissue in progressive metamorphosis, mainly where the infectious

process was most developed, in the under part of the cutis and the hypoderm. We do not need to look far for the cause of this hypertrophy. Many chronic inflammatory processes of the cutis, especially lupus and syphilis, show the transformation of spindle cells into large spider cells, and an independent fibroma formation replacing the cellular hyperplasia. The streptogenous inflammations, with their acute course, certainly present only degenerations of the connective substances, but they leave behind them the tendency to all the more active progressive changes. All the elements of the skin in turn share in the hypertrophy. The connective tissue cells are mostly converted into plasma cells; this plasmoma is distinguished from others by the great size of the cells and its equal extension through the whole thickness of the skin and hypoderm. It is enclosed between the hypertrophic collagenous bundles, and is therefore mainly disposed in lines. These often follow the dilated blood vessels, apparently, more strictly, their accompanying lymph vessels and spaces. For many blood vessels are only bordered on one side by lines of plasmoma, and these are found still oftener without any connection with the blood vessels. We may therefore describe those lymphatics of the cutis, which are seated in the collagenous substance, as the main seat and point of origin of the plasmoma in elephantiasis. But at the same time the spindle cells hypertrophy, without taking up basophilic granular masses and without withdrawing the long processes of their spongioplasm. There develope very much branched spindle cells, and, where the surroundings are still more loosely arranged, very large multi-polar spindle cells. At the same time the collagenous substance hypertrophies in the form of parallel, coarse fibrous bundles and the enclosed spindle cells again take a flatter spindle form. The hyperplasia of the collagenous tissue is likewise equally extended through the skin, with its maximum at the lower margin of the cutis. The direction of the newly formed connective tissue bundles differs from that of the original ones, but is in general parallel to the surface of the skin, that is, it is parallel to the altered cutaneous tension, which, from the swelling of the organ as a whole, has become much more equal and parallel to the surface. The general increase of the collagenous tissue reacts on the newly formed plasma cell areas, partly compressing them in different directions, partly snaring them off into rounded areas. In the former case we see, what can hardly occur in the other forms of the plasmoma, large plasma cells which were evidently originally round or cubical, bent and twisted, often with the loss of some of their protoplasm. In the completely snared-off plasmoma foci we find multi-nuclear cells, chorio-plaques and true giant cells. In the other foci there is also a striking number of multi-

nuclear plasma cells. From the form of the nuclei, I ascribed to them a mitotic development, although I found no mitosis. The great number of nuclei in the large chorio-plaques and giant cells of the snared-off areas, which lie closely together and are partly facetted, are probably amitotic in origin. Among true giant cells with acidophilic protoplasm, one sees here and there the basophilic staining, and the contours of the neighbouring plasma cells becoming indistinct. But this commencement of a regressive metamorphosis never goes any further. Altogether I have only found giant cell formation in two or three of the cases which I have examined, especially in one case from the genital region, which I owe to Herr Geheimrath von Esmarch, but in view of recent experience of their presence in the skin (*e.g.* acne), I do not doubt that they are often enough present in elephantiasis.

Mast cells are numerous, though not abundant; but their size is very striking. They are usually oval, and are situated in the middle or at the side of the plasmomatic areas.

Like other investigators, I found the smooth muscles thickened and elongated but not increased in number. Rindfleisch found, in an elephantiasic scrotum, a myomatous new formation.

The elastic fibres—here I do not agree with the statements of many other investigators—I always found almost or completely atrophic, where the formation of plasmoma and fibroma had reached them. Even the large arteries and veins partly lose their elastic tissue, where they are embedded in firm fibrous tissue.

Sharing in the general hypertrophy, the blood vessels have their lumina dilated and their walls thickened and enlarged, but there are great differences in this. While some parts of the tissue reach an almost angiomatous formation, and the capillaries are as wide as ordinary subcutaneous veins, they are, in other places, only slightly increased and enlarged. Local conditions evidently influence them. The question of their permeability is of greater interest. We find, in correspondence with the clinical observations of v. Winiwarter, quite a number of the veins filled with fresh or old thrombi, and some of them —including very large subcutaneous veins—completely closed by new growth of connective tissue. The thrombi are mostly leucocytic, they are mixed with fibrin, and some of them are adherent to the endothelial new growth. The lumina of the arteries are mostly free, and only some of them, as in erysipelas, show remains of fibrinous thrombi. Even the fluid contents of the permeable, even the dilated, vessels almost always contain fibrin, in addition to a good many white corpuscles, and finally there can always be found, with good staining, some parts of the connective tissue permeated by a network of fibrin.

This corresponds to the well-known clinical fact, that the lymph of elephantiasis is peculiarly rich in albumen, though, in view of the formation and breaking up of so many albuminous substances, nothing else was to be expected. The large plasma cells especially are frequently surrounded by tiny, broken granules of protoplasm.

The lymphatic system is also dilated, and, so far as actual walls are present, these are thickened and hypertrophic. These are only to be seen in the subcutaneous tissue. In the cutis we have a general, equal, passive dilatation of the lymph vessels and spaces, which here and there exceed the lumina of the veins; in other parts of the tissue the lymph vessels are not particularly dilated, but all the spaces are wide, and the collagenous tissue is unusually loosely arranged, finely fibrillated and œdematous. These differences in the lymphatic system are largely dependent on the stage of development of the fibrillary tissue.

At the commencement of the process the increased difficulty of the outflow of blood, with its resultant œdema, has the upper hand, and the commencing hypertrophy of the collagenous tissue is only shown in that loose, wide-meshed, soft, fibromatous character, which recalls the normal structure of the papillary body. Then the collagenous hypertrophy gradually gets the upper hand, at first only in patches. The wide lymph spaces are filled by fibrillary tissue, while the lymph vessels remain wide or are even still further dilated. But the affected areas of skin become, as a whole, hard; they are clinically perceptible as firm nodules inside the softer fibroma, for inside that the fibrous processes become fixed. At the same time, the hypertrophic connective tissue cells, which, in the œdematous tissue, were more isolated and equally developed on all sides, are pressed together, limited in their development, and flattened. Thus the skin becomes more and more fixed. There are also cases of hypertrophy of the subcutaneous fatty tissue in elephantiasis, which are to be ascribed to the integrity of the coil glands.

The epithelium only rarely remains passive in the general hypertrophy of the constituents of the cutis. There is usually a general hyperplasia of the surface epithelium, with thickening of the ridge system, and, at the same time, a hypertrophy of the individual epithelial cells, which in some preparations assume the size and appearance of the epithelial cells of the pointed condylomata. There is then a hypernutrition of the epithelium, but no inter-epithelial œdema. The epithelium of the hair follicles usually takes no part in the hypertrophy, nor does that of the coil glands, which latter only accommodate themselves, in their position and form, to the higher pressure of the surroundings.

The *first*, so-called *soft stage of elephantiasis* is consequently characterised by a hyperplasia of all the constituents of the skin, except the elastic fibres, which are never completely re-formed after their disappearance during the erysipelas, the epithelial appendages (hairs and coils), and some of the veins, which are obliterated, and further by venous and lymphatic stasis, which is gradually limited by the new formation of fibrillary tissue. The latter two phenomena do not stand in the relation of cause and effect, but are parts of the same process, and indeed, up to a certain degree, prevent each other's extension.

The second, regressive stage or *hard elephantiasis* developes insensibly from the first, the collagenous substance steadily gaining ground at the expense of the lymphatics. At first an increase in volume may accompany it. Those parts of the cutis which have remained soft, the remainder of the hypoderm, and finally even the papillary body, become the seat of a homogeneous fibrous tissue with parallel bundles. The spindle cells always diminish in size and number; the nests of plasma cells are more and more circumscribed, diminishing by resorption of protoplasm and disappearance of the lymph spaces. Then the blood vessels diminish in their calibre, the capillaries are again reduced to their normal size, and some of them, which were partly obliterated, become impermeable, while, by the breaking down of fresh thrombi, other vessels become completely permeable. The subcutaneous tissue altogether disappears. The coil glands are compressed and partly atrophic. Many hair follicles with their sebaceous glands also undergo pressure atrophy. The behaviour of the surface epithelium varies; in some cases it atrophies, in the same degree as the papillary body stiffens into an upper fibrous layer of the cutis, in other cases the arrest of nutrition is more evident in hyperkeratosis, which leads to the piling up of horny layers and—from the absence of epithelial after-growth and the extension of cornification in the pre-existing large epithelial ridges—to stalactiform horny masses. With the contraction of the vascular system there appears finally, in many places, a deep pigmentation in the upper layers of the cutis and the epidermis, which is evident in piebald spots on the surface. Thus, by the regressive metamorphosis of all the cellular and succulent constituents of the cutis and epidermis, the simple hypertrophy of the collagenous tissue leads finally to a board-like, sclerodermatic hardening and absolute immobility of the cutis, which is always thicker than normal. A persistent, irreparable condition is developed.

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Elephantiasis Filariosa. Lymphscrotum.

This fibromatosis which, from the investigations and discoveries of Wucherer (1866), Cobbold and Lewis (1872), Manson (1875), Bancroft (1877), and Magelhäes, is, in its origin, better known to us than elephantiasis nostras, is only one of the many forms of tropical filarial disease (Chyluria, soft varices and bubos of the axillary cavities, lymphatic abscesses, febrile anasarca, chylous ascites, chylous hydrocele, tropical œsophageal stricture, elephantiasis, lymphscrotum, varices and bubos of the inguinal glands, Manson). Of those results of filarial infection, *elephantiasis* and *lymphscrotum* interest us.

Elephantiasis mostly affects young people, who come in contact with water containing filaria, in the form of a febrile attack lasting for a few days; there appear red streaks of lymphangitic origin on the skin of the affected œdematous member, while the corresponding lymph glands of the axilla or groin become swollen and painful. After the attack has passed, there remains a firm swelling on the legs, especially on the thigh, where also the lymphangitic streaks tend to be most distinct. There may be ten to fifty such attacks in a year, and after each the swelling and persistent remains are greater, but the general effect and the fever, less. As the evil is localised, the local appearances increase in degree and multiformity. Now and again there is suppuration of the swollen glands and abscess formation, but there is always dilatation of the superficial lymph vessels, formation of varices which may burst or be opened by a wound, or even the œdematous skin may rupture and a lymphatic fistula develope. In both cases the result is persistent lymphorrhœa. In course of time the lower extremity is converted into an enormous, thick cylinder, with, if they are uncovered, inclusion of the feet; if boots are worn the disease only extends to the ankle. The scrotum assumes a monstrous form and weight, such as are never present in E. nost. Here the tendency to lymphangiectasis in otherwise smooth skin predominates, and that of epithelial growth and hyperkeratosis, which distinguishes many cases of elephantiasis nostras, is in abeyance.

These cases, in which, from the commencement, the formation of superficial lymphatic varices with lymphorrhœa plays a great rôle, were specially described of the scrotum, before Carter, Lewis, and Manson had recognised them as filarious, and related to elephantiasis. In them the elephantiasic thickening is less marked, but the skin shows on the surface, ectases of all the lymphatics, in the form of small vesicles, large varices and plexiform cords, which can be followed into the lymph cavities of the gland.

The pathogenesis of this disease—like that of all other filarial diseases—has been determined abroad by the work of the above investigators, especially Manson. We know that the filarial embryos, which at night swarm in the blood, are taken by a definite form of mosquito from man, and that on their death the ripe filaria reach stagnant water. From here, according to Manson, they reach the human subject by drinking, and, wandering from the intestinal canal by means of the

lymph, not the blood, again reach their old habitation, the human skin, where the female, a smooth, round worm eight to ten centimetres long, 300μ broad, has several times been found on operation.

But the pathogenesis in its finer points is represented differently. Lewis indicates three ways in which the elephantiasic and lymphorrhœic appearances may be ascribed to the behaviour of the parasite—namely, by obliteration of the lymph vessel by means of tumours containing the parasite in their walls, by perforation of the tissue by the mature filaria, and by embolic plugging of the capillaries by the embryos. Manson, on the contrary, refers only to the presumptive obliteration of the lymphatic tract. The female filariæ are always found peripherally, in the lymph vessels, not in the lymph glands; their eggs are transported from here into the glands by the lymph stream, which cannot happen to themselves. In the glands the eggs become embryos, but they only rarely cause total destruction of the lymphatic glands and inflammation. In these rare cases of *total* obstruction of the lymph glands we find no embryos in the blood, and either rupture of the lymph vessels with lymphorrhagia of the scrotum and the legs, embryos in the escaping lymph and in the glands, or elephantiasic thickening of the skin, probably with the death of the mature filaria in it. In cases of *partial* obstruction of the lymph glands there develope lymph scrotum, varicosities of the lymph glands, and chyluria, and masses of filarial embryos are found in the blood.

We see that these explanations leave much to be desired, for they are mainly founded on the hypothesis of a central obliteration of the lymph track. Such, as all experiments teach us, can never cause a lymph stasis, and certainly not such a severe one as here, any more than it can a hypertrophy of the tissue, such as meets us in the elephantiasic form. Further, we see no reason why the filaria should cause anything of the sort in the lymph glands (Manson). The eggs in the uterus of the filaria certainly measure 12-35μ in diameter, but even in the vagina of the animal, according to Lewis and Cobbold, the embryos untwist and are only 8μ broad, though 200μ long. They can thus, especially considering how smooth and active they are, peaceably wander through all the lymph spaces and capillaries of a human being. Manson indeed admits that, in most cases at least, some of them pass the lymph glands. Manson's theory therefore rests on a very slender basis.

The only certainties are the great number of the embryos in the lymph varices and lymph scrotum, their periodical appearance in the free circulation, and the presence of the female filaria in the lymph spaces of the affected skin. Since the daily periodical throwing off of embryos, which perish in the blood, is in the highest degree improbable

(Manson), they must, when they are not recognisable in the blood, be resting or detained somewhere. The most likely place, I believe, is that in which they were a short time previously to be found in numbers—namely, the circulation, and while the 8μ broad embryos always pass the capillaries of the internal organs easily, they do not so readily pass the blood capillaries of the skin, which are notoriously exposed to great variations in their calibre. Now, as a fact, the vessel tone of the skin is diminished by warmth, in bed and in sleep, while in the cold, in going about and towards morning, it again increases, and along with it, the calibre of the cutaneous capillaries alters. Here there can, indeed there must be towards morning an ever-increasing resistance to the circulation of the embryos, the more they collect in individual capillaries, and this resistance must periodically diminish toward evening, whereupon the nightly swarming of the embryos begins. It is incompatible with such a view to regard the embryos as a directly injurious factor to the tissues; for such they cannot be, for it is definitely established, that they may be found in the blood of persons who do not suffer from elephantiasis and lymph scrotum.

How they reach the blood is very difficult to explain, for all the lymph of the periphery does not pass through lymph glands, and, on the other hand, the embryos can themselves pass through the lymph glands. That they are found collected in the tissue of the lymph scrotum and the lymph varices, where the female is, does not need to be explained.

But we certainly want some explanation why progressive tissue changes and lymph stagnation are associated with their presence in definite areas of the skin. Neither the obstruction of the lymph glands (Manson), nor the narrowing of the lymph vessels by parasitic tumours (Lewis), help us much.

If we reflect that elephantiasis filariosa shows not only a commencement like lymphangitis and erysipelas, but, like these, passes into a firm œdema, and finally into a fibromatosis, this complete parallel points to the probability of a similar pathogenesis of the processes. We must free ourselves from the quite unjustified hypothesis of a primary insufficiency of the lymph track, as in elephantiasis nostras, and we can do this all the more easily, since the embryos are evidently inhabitants of the vascular system. If we assume that, as usual, the eruptive fever indicates the sudden saturation of the blood with the organisms, this primary effect, the erysipelas-like affection of the leg, for example, can only indicate that, in contrast to the rest of the capillaries of the body, the organisms have, here in the skin, left the blood capillaries and penetrated into the tissue itself. The varying calibre of the cutaneous capillaries makes the collection of embryos in

them easy, especially in those more exposed to gravity, the dependent parts of the body (leg, scrotum, arm, mamma). Thus we begin to see why it is that certain regions of the skin are specially affected. In the skin we know that the maturation of the individual filariæ takes place. It is premature to assume, that in a disease which has lasted years, the mature filariæ which are found at an operation are the same ones which originally wandered from the intestines. With all respect for the ingenious experiments of Manson, I hardly believe that the maturation of the embryos in man is excluded. The maturation in the mosquitos has certainly an important significance in the spread of the disease from one person to another, but not for that inside the body of the patient. The throwing off of embryos of these new, mature filariæ, and their migration through the lymph vessels into the blood, explains very satisfactorily the new attacks of fever and the concomitant swelling of the glands. There at once takes place a new stagnation of the embryos in the same capillary regions as at first, and a partial immigration into the cutaneous tissue, with fresh affection of the skin, which prepares the way for fresh maturation and fresh periods of fever.

All this is not an explanation simply made up for elephantiasis filariosa; it is only a summary of the processes, which we have to assume in all infections, which, in addition to a chronic dermatosis, show a periodical immigration of the organisms into the circulation, *e.g.*, as in leprosy. Only in filariosis we are dealing with a cycle.

But it explains why the general affection always gradually diminishes in severity, although in certain cases the embryos persist in the circulation, and why in other cases the dermatoses, in definite regions, assume such gigantic dimensions, while the embryos disappear from the blood.

The first fact is explained, as in many other infectious processes, by the body becoming accustomed to the by no means powerful poison, to a gradual immunisation, a transition of parasitism into symbiosis. This does not exclude the fact that the sudden introduction of a large number of embryos into the circulation at first induces symptoms of fever.

The second fact is explained by the nature of the skin affection, which is accompanied by lymph stasis, and leads to proliferation. The first symptom points to a primary disturbance of circulation, of the character of venous stasis. That must be supplied by the first invasion of the filaria. As this is followed by clinical erysipelas-like symptoms, the penetration of the filaria into the skin must lead anatomically also to erysipelas-like changes, that is, to a fibrinous inflammation. And since the persistent œdema of the cutis after erysipelas is to be

ascribed to undissolved fibrinous thrombi in the capillaries and veins, that in filariosis may be explained in the same way. But we have, more certainly in elephantiasis filariosa than in elephantiasis nostras, a persistent cause of tissue hypertrophy in the constant presence of filariæ in the tissue.

According to the predominance of tissue hypertrophy or lymph stasis, we divide the cases of tropical elephantiasis into the elephantiasic and the lymphorrhœic. Only the former, in which the element of lymph stasis is minimal compared to the great collagenous hypertrophy, correspond to elephantiasis nostras. In them the playground of the embryos is limited to the few succulent areas which remain, while in the lymphorrhœic form the filaria may swarm all through the hypertrophic cutis and subcutis. This explains very clearly, what Manson ascribes to the rare obliteration of the glands, why in cases of elephantiasis the embryos are often absent in the blood, while in lymph scrotum they may almost always be recognised.

The lymphorrhagia of the lymph scrotum takes places from the ampullated, swollen dilatations of the papillary lymph vessel termini, which are clinically visible as vesicular, soft protuberances.

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(β). *With the power of Generalising.*

Frambœsia (*Yaws*).

A specific, chronic, general disease, conveyable by inoculation, which appears endemically in certain tropical regions (Africa, Indian Archipelago, West Indies), particularly in coloured people. The disease may affect the patient repeatedly, does not interfere with his general health, but leads to infectious growths on the skin and mucous openings (lips, nose), of peculiar form and remarkable hardness and duration. Inoculation, which after fourteen days leads to a soft ulcer covered with a crust, is followed three or four months later by a gradually appearing eruption, with fever and general swelling of the glands. It consists of papules, the size of mustard seeds, which slowly extend in breadth and height, and are covered by a yellow crust, with red dots. No part of the skin is exempted ; around the anus, mouth, penis, fingers and toes the papules form confluent walls. Now and again they extend in a circinate form. On the scalp they do not lead to loss of the hair. The growths, which at first are painful, later become indolent and harder, and finally, when they have a diameter of about three centimetres, are snared at the base. After removal of the crust they show a strawberry-like, red, moist surface. They are very resistant, preserve their form on the contact areas (anus, axillæ), as a rule do not ulcerate, or only

on the sole after irritation, and they remain dry, even in the nostrils, mouth, and in the axillæ. During the progressive stage they have a broad, dark (in white people, red) halo ; when, after months, absorption begins, they shrink and become darker, their halo paler ; they are covered with white scales, and finally, often after years, they disappear without leaving a scar, but only pigmented spots.

Charlouis, to whom we owe a very good clinical examination of framboesia, found in the smallest papules the horny layer thickened up to three times its original thickness, in the older ones the papillary prickle layer and the papillary body much increased, passing at the periphery gradually into the healthy tissue, the vessels very much distended, the cutis and the enlarged papillary body infiltrated with leucocytes, and the crust consisting of sebum, epithelium, and leucocytes. As the tumour enlarges, the dilatation of the vessels and the increase of cells extend deeper into the cutis. The sebaceous glands are greatly enlarged, their secretion gives the yellow colour to the crust. The coil glands are dilated, their epithelium enlarged. The hairs are unaltered, only their follicle walls are infiltrated with cells: the arrectors are enlarged. The leucocytic nature of the cells which infiltrate the tumour, the author deduced from their mainly perivascular position.

Pontoppidan only gives a very short description of the nodules, which, according to him, consist of granulation tissue of similar formation to that in lupus or gumma. This is placed superficially under the altered and infiltrated prickle layer, consequently in the papillary body. Pontoppidan places the actual seat of the affection in the prickle layer, and remarks that it possesses a more superficial character than is usually assumed, and shows no proper secretion of pus.

The generally dry and firm character of the growth points to a great share of the epithelium in its formation. This is the most striking feature in a nodule, which I got through the kindness of Mr Malcolm Morris. It certainly does not represent the first painful stage, with increased secretion, but the indolent, dry, chronic stage of the growth ; nevertheless, all the conditions are very characteristic.

At the border of the button-shaped tumour, which reaches about a centimetre above the surroundings, their commences an epithelial growth, which rapidly leads to an excessively wavy papillary body. The number of the papillæ is not increased by the in-growth of the epithelium, but they are increased in length ten or twenty times. The resistance which the papillæ present to the growing prickle layer must consequently be abnormally high, as must the resistance "de tergo" of the horny layer. The increased papillary resistance is shown by a distinct dilatation of the blood vessels in the neighbouring skin as well

as in the papillary region; the increased resistance of the horny layer, by a marked hyperkeratosis, with heaping up of a thick horny covering. The acanthosis consequently leads here, as in most pointed condylomata, to a mainly *inter-papillary* prickle layer, while the supra-papillary layer, in proportion to the whole elevation of the tumour, remains insignificant. This explains the ready appearance of small epithelial hæmorrhages, which form the red dots in the crust; otherwise the prickle layer shows no peculiarities. As one would expect from the chronicity, mitoses are not present in increased amount. Where the horny covering has the character of a dry scale, especially in the middle of the tumour, the granular layer is well developed, and occasionally excessively broad. In other parts, especially at the periphery, the granular layer has partly or completely disappeared, the basal horny layer is partly granular, split into lamellæ, contains fibrinous coagula and wandering cells, and is thus converted into a fibrinous crust. This transformation is always accompanied by a permeation of the under-lying prickle layer with wandering cells, dilatation of the inter-epithelial spaces, and deposit of fibrin in them. I will return to this limited and superficial leucocytosis and sero-fibrinous inflammation and its significance.

Along with this distinct acanthosis and hyperkeratosis of the surface, there are progressive changes in the cutis. The epithelial growth rests on a solid cellular infiltration of the cutis, consisting mainly of typical large plasma cells. These surround, like a mantle, the individual epithelial processes, and extend, in thin cords, into the individual papillæ. Underneath the epithelial growth they run together into a uniform plasmomatic layer, which extends outwards and laterally, in scattered, single foci and cords. These mainly accompany the large dilated veins, but show no relation to the epithelial appendages, the coil glands or hair follicles. The former have usually a dilated lumen, and some enlarged epithelium, the follicles are quite normal, and the hairs penetrate, without change, both the plasmoma and the acanthoma. There is never degeneration of the plasma cells; the tumour consequently represents the purest type of plasmoma tissue.

The spindle cells of the cutis are enlarged, but not distinctly multiplied. The collagenous tissue shows neither progressive nor regressive changes. Only at the plasmomatous areas, it is, as usual, rarefied and reduced to a fine fibrous net. The elastic tissue is also preserved, except at the plasmomatic areas, the mast cells are not notably increased in number.

The pigment requires special attention. The preparation, which evidently comes from a coloured man, shows, all round, a deep pigmentation of the basal prickle layer. In the growth, the pigmentation is

less, and is equally distributed in the very much increased epithelial margin. Scarcely anywhere is the branched, antlered, pigmentary stream in the interspinal spaces so beautifully seen. Nuclear enclosures are also present, and we have thus the most typical "pigment cells." But on closer observation we see that the nuclei are epithelial nuclei, and further, that completely unaltered epithelial cells are enclosed in the streaks of pigment, and that this combination forms the so-called pigment cell. There are also "pigment cells" which contain two or three nuclei, according to the number of epithelial cells surrounded by the stream of pigment. As a fact, we have only a stream of pigment, itself without cells, but enclosing the epithelial cells.

Consequently, the formation of the frambœtic nodule as a whole is very simple; it is a plasmoma of the cutis, complicated with great epithelial growth and hyperkeratosis. In the absence of all degenerative changes (giant cells, homogenisation) it is still more simply constructed than a syphilide, which in many points it resembles. The general affection pursues the same course, but the eruption is more persistent. Of the syphilides it is most like the condylomata, but is distinguished from them by the greater dryness of the skin and the more advanced cornification. This also explains the hardness and resistance of the papule. Its strawberry form, after removal of the crust, is the result of the great increase of the papillary body, and its thin covering with supra-papillary prickle layer; it is thus ultimately due to the increased dilatation of the vessels, which accompanies the papule formation.

From the constitution of the eruption, at the height of its development, it is evident that the cellular infiltration does not consist of leucocytes but of resistant plasma cells. It is then very improbable that the first period, which is accompanied by swelling and pain, is caused by a local leucocytosis, as Charlouis assumes. Plasmoma formations tend to appear as such, but they may at the commencement, like syphilis, very well be accompanied by an excessive dilatation of the vessels and a sero-fibrinous exudation, which latter is gradually reabsorbed, leaving behind the dry plasmoma nodule. But, as in syphilis (and in lupus), organisms from without very easily take possession of the fibrinous crust, increase the softening of the horny layer, and cause a superficial, local leucocytosis, and this may also occur here. It is of course clear that the "germs" of frambœsia must be looked for in the first stage of the eruption and in the cutis.* The streptococci and the packet cocci, with which the scale swarms, are consequently to be definitely regarded as deuteropathic. But they may very well contri-

* In my case none were discovered with the ordinary methods, and were hardly to be expected.

bute to the crust formation by attracting fibrinous exudation and leucocytes. As a fact, these are only found in certain places, in the neighbourhood of individual papillary apices, where they closely permeate the prickle layer, and induce abscess-like areas in the cornified layers. If the emigration of leucocytes was part of the affection, we should find them in the depths of the tumour, or at least around the large sub-papillary veins and capillaries, where they are completely absent. The very dry character of the affection permits the recognition of this local, limited leucocytosis and fibrinous exudation as a secondary infection, better than in many syphilides; it has no necessary connection with framboesia.

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Mycosis fungoides.

Under this name, which was introduced by Alibert, even after excluding certain dermatoses which present some resemblance to it, especially the leukæmic growths and the sarcomata, there are still several conditions described. These so far correspond, that in a great majority of them, there appear slowly developing infiltrations and tumours, especially on the upper half of the body, which, unlike sarcomata and carcinomata, present spontaneous improvements and aggravations, but finally lead to death from marasmus or sepsis.

The growths either appear on perfectly normal skin and are normally coloured, or are reddened, of a moderately doughy, soft consistence, may reach the size of plums, and, as they grow, may be snared at the base. They only rarely and transiently ulcerate; but marasmus gradually sets in (the form of Alibert and Vidal, of which I saw one case).

Or they form, especially on the trunk and the neck, dry, scaling, yellowish or brownish spots, the size of a shilling to that of the palm of the hand, which may last for months, and then pretty rapidly develope into large nodes of the same size as the spot was. This form ulcerates readily, and marasmus soon ensues (a case of my own).

Or, finally, and this is by far the most frequent occurrence, there exists a *long, varying, preliminary stage*, in which dry, itching, here and there moist, crust-forming, flat infiltrations, or deeper lying, widely spread nodules appear, which leave the epidermis intact; they become elevated, enlarged, and sometimes disappear again, until the whole body is covered by these curiously-figured infiltrations, with the frequent exception of sharply-margined areas of normal skin, corresponding to vessels. In the course of one or two years all the spots are transformed into deeper infiltrations, of which the largest reach one or two centimetres above the epidermis. The summits of these infiltrations, which by no means necessarily correspond with the original spots, readily ulcerate and very often give origin to secondary infections, to which the patients, if the main

disease do not heal, usually fall victims. In this form the whole vascular system of the skin has evidently been long affected, before in certain places that height of the infiltration is reached, which we recognise clinically as tumour formation. The lesser degrees of the infiltration have, on account of their resemblance to certain eczemas and to lichen urticatus, been described as "eczematous or lichenoid" stages. It is more correct to distinguish a *slowly progressive first*, and a *rapidly progressive, second* stage, for the greater affection of the epidermis by no means belongs solely to the early symptoms, and it may be altogether absent.

In addition to this tendency to universal extension in figured form (though in a symmetry only regional) this variety of mycosis fungoides has the peculiarity, that it begins on the head, and from here affects the neck and upper extremities, then the trunk, and last of all the legs. Along with it, there is a pronounced tendency to inflammatory seborrhœic conditions (eczema seborrhoicum, seborrhœic warts ; at least this was striking in all my cases. This third and most frequent form is therefore possibly, on account of its *complications with true eczema*, its advance from above downwards and its tendency to widespread superficial extension, to be regarded as a mixed infection with seborrhœic catarrh of the skin. To this form alone relate my own histological investigations on Mycosis fungoides, of which I now give the results.

The flatter infiltrations of the first, interrupted, progressive period are, clinically and histologically, distinguished from each other by the lesser or greater affection of the epidermis, while the changes in the corium always show the same character. These latter consist in a progressive growth of connective tissue cells, first around the capillaries in the papillary body and the sub-papillary vascular net, then in the whole papillary body equally, so that in time the upper part of the cutis, as far as the upper vascular net, shows a marked cellular infiltration, all parts being affected alike. In this the cellular infiltration is distinguished from that of syphilis, which reaches its acme around the blood vessels, and that of tuberculosis which avoids them.

Then the spindle cells, as they swell up, only exceptionally, and only at the commencement, form the easily recognisable, typical plasma cells. These, so characteristic of the granulomata of syphilis, tuberculosis, leprosy, etc., are never properly developed in mycosis fungoides, and herein lies the main characteristic of this dermatosis, compared to the true granulomata. In the plasma cells, which rarely appear, we see that, even in Mycosis fungoides, there exists at the commencement a certain tendency to the formation of plasma cells (something like Ulerythema centrifugum), but that certain conditions must interfere with their complete formation and persistence. And these conditions are at once evident with a good protoplasm stain. The cellular infiltration is, from the commencement, densely permeated by a mass of granular, multiform particles, which, by the resemblance

of their colour to the granules persisting in the cells, show their origin from these cells. What takes place in patches, and occasionally in the true plasmoma during resorption and healing, takes place here all along, and accompanies unceasingly the process of growth. Thus the saturation with protoplasmic particles from the cells of the infiltration becomes as important and characteristic a symptom of the histological appearance of Mycosis fungoides, as the associated spontaneous arrest is of the clinical appearances of the disease. (Front., Fig. 3.)

It is the result of this peculiarity, that all the cells—with the exception of a few true plasma cells—are indistinctly margined and very multiform, a peculiarity which later, with the formation and breaking down of cells, appears still more distinctly. It is, therefore, hardly necessary to describe their form. Some resemble the marginal spindle cells, only the nucleated centre of the cell being definitely swollen, without its dendritic connection with the neighbouring cells by fine processes being interfered with. Others may resemble typical or spherical plasma cells, all the processes being drawn in, and the cells taking the basic colours more distinctly. As to the presence, form and stain of the nucleus, hardly any cell resembles its neighbour. This is not due to a general saturation with chromatic substances from the nuclei, for these rather show an increased stain, but rather to a very regular mitotic division of the nuclei, for, in addition to the mitoses, the nuclei in the preliminary and after-periods are very deeply stained. The frequency of mitosis in this growth is in great contrast to its relative rarity in the most cellular, true plasmomata; we will therefore not go far wrong, if we recognise the reason of this difference in the want of the formation of true plasma cells in Mycosis fungoides.

The mitosis by no means always goes on to division of the cell, but rather leads to the formation of multi-nuclear cells, which are very sharply distinguished from the pale, multi-nuclear cells of the true plasmoma, since they are not developed from plasma cells. The main difference consists in the fact that the multi-nuclear cells of Mycosis fungoides have a perfectly normal, frothy, certainly not homogeneous protoplasm, that they are very indistinctly margined, usually being sharply defined only on one side, and that they are frequently connected by processes with neighbouring cells. Further, we find in them, now and again, mitosis, which is never present in the homogenised, multi-nuclear cells of tuberculosis and syphilis. (See frontispiece, Fig. 3.)

The number of nuclei varies extraordinarily; cells with two to four nuclei alternate with true chorio-plaques, containing ten to twenty nuclei. These are mostly quite irregularly arranged, and the cells, in

spite of the number of nuclei, do not recall the appearance of tubercular giant cells, but rather resemble the myelo-plaques of bone. Further, they are very irregular in their form, are beset with processes and never rounded and sharply margined. But the main difference, here also, lies in the fact, that the protoplasm does not show the same degeneration into a peculiar, fine reticular substance.

As already indicated, some giant cells are exceptional, and in their sharp contour, their round form, the marginal or garland arrangement of their nuclei, indeed, even in a similar change of the protoplasm, actually resemble the giant cells of tuberculosis and syphilis. But, such are found only occasionally and only in the commencement of the process, so that their existence only confirms the above-mentioned rule, that the growth at the commencement takes a step in the direction of a true plasmoma, but gets no further.

While the papillary body is thus filled with a dense net-work of proliferating cells, the collagenous substance remains apparently normal. It neither shows, as in the syphilitic plasmoma, a tendency to individual growth, nor does it at once vanish before the cell growth, as in lupus; here we have a third main distinction from the two most important infectious plasmomata. The result is, that the cellular infiltration, however great it be, and however much it distend the epidermis, always retains its original arrangement. It neither arranges itself in the form of streaks between swollen collagenous tissue, nor does it fill up spherical, new formed cavities in it. Rather the affected areas of skin simply swell as a whole, fill more or less all the lymph spaces, and show swelling or diminishing cords, which are connected by processes on all sides to the neighbouring cells; *but the connection of the tissue is never torn or its arrangement altered.* Consequently the growth has neither the hardness of the syphilitic infiltration, nor does it reach the softness of lupus tissue.

The blood vessels in this first stage of mycosis are always dilated, but, with the exception of accidental mitosis, show no changes of the endothelium. The lymph vessels and spaces are mostly considerably dilated, so far as the persistent cellular growth has not completely closed them for the time. They are never permanently closed, for a rich stream of lymph always washes the collections of cells, carrying away fragments of cells, and here and there complete ones. But there are often seen irregularly distributed collections of ten to twenty closely packed, mostly angular nuclei, which, with a low power, look like giant cells or collections of leucocytes, but with a high power, are seen to be collections of the ordinary cells, which are characteristic of Mycosis fungoides. These cell nests are often found in the papillæ, where they are in relation to the cell nests in the epithelium, to be immediately described.

During these changes in the cutis, the epidermis is not inactive, not at least where the infiltration of the cutis reaches the epithelial margin. Clinically, indeed, the epithelial changes complete the tumour-like character of the affection. There is first a proliferation of epithelium, which is indicated by numerous mitoses, and by enlargement of the epithelial ridges and the supra-papillary prickle layer, and there is, in addition, a dilatation of the lymph spaces of the epithelium, which take up only a small number of leucocytes, but an increased amount of fragments of cutaneous cells, and there is often an enlargement of the epidermic cells themselves. The transitional layers and the horny layers are at first normal. This corresponds to the slightly papular, but still smooth growths.

As the condition advances, the inter-epithelial œdema increases. There develope at certain points inter-epithelial vesicles, or a spongy distension of the prickle layer, whereby the intercellular passages are transformed into a multi-locular system of cavities, with expanded and stretched epithelium between. Thus, by simple œdema, merely accidentally, and without any relation to the whole process, there is developed that appearance, which for years has been ascribed in such a random, wholesale manner, to all possible vesicular processes, in which it is never found. Still more remarkable, although not limited to Mycosis fungoides, are solid connective tissue cell nests, of the same type as the breaking-down cutaneous cells,* which appear to be partly enclosed in the prickle layer, partly connected by a neck with corresponding cell nests at the apex of the papillæ, or at other parts of the cutis margin. Many of the apparently isolated areas in the prickle layer may be only lateral sections of the latter variety, but the possibility of a snaring of these free cellular areas by the epithelium is not to be disregarded. In addition to these cell-nests there are also spaces in the epithelium, which contain the smaller cell balls, and thus we have a peculiar form of vesicle, whose contents are not leucocytes, but migrated, mitotically divided, cutis cells. The luxuriant growth and loose cohesion of the latter, along with the presence of a rich lymph stream and wide epithelial spaces, makes this appearance comprehensible, and it is present also in limited spots in other conditions, under similar circumstances. (Ulerythema centrifugum, Erythema bullosum vegetans.)

To this increase of the inter-epithelial œdema of the prickle layer, there sometimes corresponds a transitional layer, free from keratohyalin, and a nucleated, thickened, loose horny layer; often the œdema stops suddenly at the granular layer, and this and the horny layer are normally formed and simply hypertrophic. There thus result clinically,

* L. Philippson has found mitosis in these nests.

sometimes scaly, sometimes simple, dry, papular conditions; the vesicles of the prickle layer are sufficient to account for occasional weeping.

While the purely secondary changes of the epidermis explain the different external appearances of the affection, the striking change in volume and the occasional disappearance are simply due to the fact, that two processes are constantly present: *the solution and breaking-up of the cell protoplasm and the luxuriant mitotic proliferation.* If the latter, from unknown reasons, diminishes, the disappearance of the infiltration is the natural result, and its reappearance indicates predominance of production over the constant destruction. The larger number of well-developed plasma cells, which is seen in some pieces of skin, can only be the result of less destruction of the cells. In contrast to the often recognised resistance of the true plasmoma, we may here, in Mycosis fungoides, speak of a "peculiar frailty" of the cell protoplasm, while the nuclear substance certainly possesses an unusual power of reproduction.

Compared to the first changeable stage, we find in the second or final one a constant increase in the infiltration, often to very large, lobulated, always rounded, gently elevated growths. Microscopically, we find the same process as at the commencement, only the growth is much greater than the breaking down. The collagenous tissue still behaves passively, and yet there is an increase in the consistence of the tumour, due, however, only to increased tension. Microscopically, this is seen in the columnar, or at least more regular arrangement of the masses of cells. As before, these only occupy the papillary body and the upper part of the cutis, and stop abruptly at that margin, as is beautifully shown by staining the elastic fibres, which first begin to form a dense mesh-work where the growth stops. The papillary body, with its circulation, may, by the enclosure of so many cells, be swollen to five or ten times its normal thickness. The epithelial covering is consequently thinned, as are the fine stretched ridges, which tend to divide the upper part of the growth into regular sections. Between the stretched epidermis and the remains of the cutis the cell masses are now arranged in coarse bundles or columns, which stand almost perpendicularly.* Vessels, follicles, glands, all the enclosures are thus perpendicularly arranged and stretched.

Otherwise the construction of the tumour remains the same. Here also, we have, here and there, denser cell nests and more plasma cells than usual. Mast cells, as in all œdematous processes, play a very unimportant rôle; they are as rare as at the commencement. There are still four points, which are characteristic of the terminal stage of

* Like the cell masses of large nævi.

Mycosis fungoides; the *œdema of the surfaee*, the *after-growth of the epidermis, the hyalin degeneration of the vessels* and *the ulceration, with immigration of foreign organisms.*

In all stained sections of larger and older nodules we find, here and there, often all through the section, unstained or paler parts, which occupy the uppermost parts of the cutis, and are seen with a high power to be relatively poor in cells and very œdematous. The papillæ here have a knob-like form, are succulent, and compress the atrophic ridge system of the epidermis into very thin lines. The capillaries and lymph vessels are very much dilated; the lymph spaces and their cellular contents have largely disappeared. This œdema is probably to be mainly regarded as a stagnation œdema, caused by the pressure on the cutaneous venous capillaries of the dense cell masses. Similar appearances are seen on the surface in other infectious growths, *e.g.*, syphilitic, where they exist for any length of time. As usual in such cases, the connection between the œdematous papillæ and the epidermis is very slight, so that trifling injuries are sufficient to strip the epidermis from the cutis.

In other parts of the growth we recognise epithelial proliferation, which may here and there acquire striking dimensions, and occasionally grow through the cell masses of the cutis down to their base. More frequently it is only seen as a thickening and extension of the previously atrophic ridges. The lanugo hair follicles have mostly already perished, and can therefore only rarely share in this secondary growth, but the diminished follicles of the scalp may do so, and cystic formation is common in them. Everywhere we can recognise, in these deep epithelial masses, a tendency to take up whole nests of cutis cells, like small abscesses; more rarely we find fibrinous vesicles with a few leucocytes in the epithelial processes.

This epithelial growth is by no means a constant phenomena, and is usually limited to certain areas. It is to be completely separated from the early symptom of more general acanthosis. The latter is evidently a symptom of the disease itself, caused by the very superficial situation of the new growth, the other probably owes its origin to secondary processes. In my cases there concur growth of the surface epithelium, œdema of the transitional layers and formation of eczematous crusts, which are closely packed with characteristic morococci. I am therefore inclined to regard this secondary acanthosis as a symptom of the concurrence of seborrhœic eczema.

In contrast to the epithelium of the surface and the follicles, that of the coil glands remains passive during the whole course of the disease. Not even the connective tissue cells around them, which

usually share, in all cases, in plasmoma formation, are in any way seriously involved. The disease stops short above the zone of the coil glands.

Philippson has recently pointed out the presence of thrombi in certain vessels of the growth, and a hyalin degeneration in their neighbourhood. The stretched, ascending branches of the blood vessels, usually those lying at the border next the superficial œdematous zone, are filled with hyalin masses, and are partly dilated, partly collapsed. The endothelium is either well preserved or no longer stainable, and, in the latter case, an immediately adjacent zone, of the breadth of two to four cells, is converted into a homogeneous, clear, hyalin mass without stained cells or nuclei, so that, instead of vessels, only solid cords penetrate the growth. Now and again leucocytes are mixed with the thrombi or larger cells, probably detached endothelium.

This belongs to a later stage of the disease, and it must remain questionable, whether this interesting change in the vessels has anything to do with the embolic origin of the disease. Micro-organisms, which are otherwise numerous, I have never actually found in the thrombi, except in one tumour, where the whole lymphatic system was secondarily filled with foreign micro-organisms. That the thrombi may increase the superficial œdema of the growth is certain, although the obliteration of a few vessels is over-compensated by the dilatation of many collaterals; but the œdema is a widespread affection, quite independent of the thrombosis.

We must finally consider the secondary immigration of micro-organisms, which has given origin to much discussion. In the examination of one single tumour, in whose lymphatics one single kind of organism is very prominent, one is always inclined to ascribe to that organism some significance. But if one examines, further, several tumours of an individual case, and finds in the different ones different organisms, here cocci, there bacilli, in a third tumour two or three organisms at once, the secondary position of all of them is easily seen. From their numbers they are probably accidental visitors. Naturally they are oftenest found in ulcerated tumours, but not exclusively so. I have recognised micro-organisms in well cornified older tumours, bnt it is always possible in such cases that they had been previously ulcerated. An enumeration of these organisms is, on account of their multiplicity, of little use, and I content myself with mentioning them.

The most important fact is the *facility* with which the tissue of Mycosis fungoides is invaded by strange parasites; it seems almost to stand alone in this respect. It behaves almost like an artificial medium

without any life of its own, and without any vitality to oppose that of the parasites. As a fact, the lymphatic system of the growth is constantly saturated with breaking down protoplasm, and probably this forms a very favourable medium. So far, the distinction between the true plasmomata (syphilis, tuberculosis) with their persistent and characteristic cell types, and Mycosis fungoides, with its frail and characterless cells, is as great as possible.

Secondly, we must consider the seat and the degree of the secondary growth. Some organisms are found only at the surface, and, by inducing necro-biosis, lead to loss of substance and extending ulceration. Others, among which I have found both bacilli and cocci, the latter, in one case in enormous collections, penetrate the tumour all through, without apparently having the slightest disturbing effect on the tissue around. Others again form around them large necrotic areas in the substance of the growth, where all recognisable structures disappear; this I found caused in one case by streptococci. It is evident that thus not only may rapid breaking down of the whole tumour be induced, but that general septic infection, to which most patients are liable, will not long remain absent. We may learn from these observations the practical rule, that patients suffering from Mycosis fungoides have rather to be guarded from secondary parasites by external antisepsis, than from the germs of their own disease.

It would certainly be premature to say, that none of the organisms yet observed is the true cause of the disease. But it is necessary that it shall be constantly found in the first stage by cultivation or by the microscope; then we shall be able to forego the experiment of the artificial production of Mycosis fungoides.

Since I have never found ulcerated tumours which do not contain numbers of micro-organisms, I incline to ascribe the final ulceration mainly to these secondary infections. In the normal development of the disease, necroses, as in tuberculosis, do not occur, and internal reasons for the death of larger parts are not present; the thrombosis of individual vessels of the skin is easily compensated. But. the œdema of the papillary body leads to ready elevation of the atrophic epidermis, and opens to the organisms of the outer world a magnificent field. Nevertheless, there usually only developes a widespread saprophytism, with slow destruction of the surface, and usually the patients perish much sooner from the, thus acquired, general sepsis, than the tumours do from the local.

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Syphilis.

1. *General Review.*

The syphilides, *i.e.* all those affections of the skin which appear in the course of constitutional syphilis, and are caused by it, have always formed a class of dermatoses, etiologically indeed, uniform, but clinically excessively multiform. In so far as the explanation of the external multiformity must be sought and found in the anatomical structure of the syphilide, pathological histology has to show that there is one factor common to all these eruptions, and that the clinical individual peculiarities are so many variations of the same type.

The centre of all is, of course, the syphilis germ, which is the nucleolus of the anatomical nucleus. But even admitting that the bacillus, which is found by Lustgarten's method, is really the actual germ, we are far from being able to construct, with its help, as in

tuberculosis and leprosy, a scheme of the manner of the development of the pathological details. It is as yet only a very troublesome curiosity among the enormous collection of anatomical facts regarding the syphilides. I will therefore attempt the description of the syphilides without reference to it, only mentioning it as the, as yet, most trustworthy candidate.

The anatomical unity will be apparent to the reader from the description of the individual forms, but there is a series of facts which cannot be mentioned there without constant repetition, and which may therefore be shortly treated in common at the commencement. These are those peculiarities of the syphilide which we tend to regard, from purely clinical observation, as the invariable signs of all, or at least of most syphilides, peculiarities of form, consistence, colour, and progress. These specific marks of the syphilide, these oases in the desert of an unending multiformity, are especially of value in explaining, so far as they go, the anatomical facts.

The form of the syphilide is necessarily the result of that reaction of the skin which follows directly on the implanting of the syphilis germ in the skin. It is always round or oval, never much larger than a lentil, and only in rare cases much less. The round form requires no explanation; it is any departure from this natural form of any zone of reaction—as in the polygonal lichen papules—which requires to be explained. But it is otherwise with the size and the coalescence of the reaction areas. We know that, during the eruptive period, the germs of the disease in all acute exanthems circulate in the whole skin, and yet the rashes only appear at limited spots. To the first invasion, the skin of most healthy men is, with the exception of a few places, immune. If the syphilis germs, untreated, get time to become more vigorous, then the resultant papular exanthema shows that the skin is no longer immune, the germs spread everywhere, flourish in the skin, and produce the papular syphilide. The longer the case is untreated, the more spots are affected. Since these are not simply extensions of the original ones, but appear between them and show the same, normal size, they are to be ascribed to new syphilis germs, which induce a reaction around them. But since, in spite of the absence of treatment, the reaction areas never all run together, since there are always free parts of skin, and the chronicity of the malady excludes accidental preservation, we must always have some areas of the skin, immune even to the most active invasion.

And this immunity is always increasing. Even the most severe secondary eruptions ultimately disappear without any treatment, the areas of reaction disappear, after they have—at least in most places—overcome the syphilis germs. Then follows a period of apparent com-

plete immunity of the skin, until the next invasion of the intensified poison. In these successive attacks, however, the skin is notoriously attacked in less extent, it is immune over larger and larger areas; the tertiary eruptions are always more localised, and finally we have a complete immunity—naturally much sooner under appropriate treatment than when left alone. My observations agree with Neumann's in making it probable, that this acquired immunity corresponds to an evident change in the structure of the skin, especially to an alteration of the vessels.

The want of continuity of the syphilitic eruptions is explained by this, at first great, then diminishing, and finally very marked immunity of the skin. From the very regular size of the elements of all syphilides, young as well as old, we must assume, that they depend on a definite number of syphilis germs (one or several), which have no longer power of multiplication. For, did a further multiplication take place inside the reaction area, the areas would extend serpiginously, which they do not usually do. No doubt the serpiginous nature has been regarded as a particular character of the syphilides in general, but it is not so. It is only added to a few secondary and tertiary forms, and these possess a peculiar type, both clinically and anatomically, which lead us to regard them not as simple syphilides, but as mixed infections with inflammatory dermatoses of some other sort.

It would directly contradict the main law of the syphilides, that of the relatively great immunity of the skin, if every syphilide possessed in itself the power of extending in an unlimited serpiginous manner, of passing from less immune to more immune areas of skin. For this some favouring additional cause appears to be necessary, especially an inflammatory skin disease, having in itself the power of extension, like seborrhœic eczema, which perhaps removes the acquired histological cause of the immunity. At all events we have striking examples of the fact that a simple papular or tuberous syphilide may become serpiginous owing to such an extending cutaneous catarrh.

If we withdraw all these mixed forms from the syphilides, those which remain are at least less multiform.

Certain gummata form a striking exception, for they appear, like the tubercular gummata, to extend and to undermine the surrounding tissue, and lead to its liquefaction. But as a fact we have there only an extending liquefaction, the gummatous change has been present for a long time in a circumscribed form, much more extensively than was apparent. Indeed the kidney (horse-shoe) shape, which is characteristic both of the tertiary serpiginous form and the gummata, is only the mark of the persistent immunity of the surrounding tissue, which, at the side opposite to that where the cause of the extension exists, projects a wedge of healthy tissue into the tertiary affection.

Roseolæ, papules, tumours, and gummata, of rounded form and lentil size, are then the very uniform elements, which compose the simple syphilide. With them the neurosyphilides in conjunction with the vessels of the skin, already described, have nothing in common. And so the number of the multiform syphilides is further diminished, if the ring-, cockade-, and net-formed, polycyclical forms of the neuro-syphilides, which have developed on a special base, are separated from them.

Before I leave the form and the method of extension of the syphilide, I will only note in parenthesis, that the existence of mixed forms explains much which was peculiar and obscure, in particular the topographical differences in universal syphilides, and the extraordinary and striking duration and obstinacy of certain forms, whose remote cause was over-looked.

More striking than the multiformity is the colour of the syphilide. We distinguished a specific copper colour and a raw ham colour; both comparisons are, in many cases, happy. As yet, unfortunately, we have no anatomical explanation of them; for the view that the pigmentation which accompanies almost all syphilides has anything to do with the peculiar colour is as little true, as the ascription of it to the transudation of the hæmoglobin-containing serum, which probably causes the pigmentation. Anatomical examination of the most perfect coppery papules usually shows, neither in the epidermis nor in the cutis, more pigment than normal, usually indeed less, as is readily seen when the papules appear on pigmented parts of the skin. And further, against the share of the pigment in the specific syphilitic colour is the fact that it does not appear in deeply-pigmented and equally inflamed growths, naevi, &c., while there should be a proportion between the amount of pigment and the amount of the colour present, which there is not. The hæmoglobin-containing serum, on the other hand, supplies, as we very well know, the play of colours of absorbing hæmorrhages, and is only externally visible when present in large amount.

If we empty a coppery papule by pressure, it shows a brownish yellow, somewhat transparent tinge, very like that of a lupus nodule. We see, then, that the coppery colour is a combination of the colour of the blood and the colour element of lupus. This colour element is due to the absence of collagenous substance and the presence of plasmoma; the former gives the transparency, the latter the honey-like, yellowish brown colour. Now the syphilitic papule is also an almost pure cellular plasmoma, but it is permeated by blood vessels, which in lupus are usually absent. While the superficial capillaries add their blood-red to the yellow of the plasmoma, the blood-red of

the deeper vessels shows through in bluish tones, as is always the case when dark masses are visible through an opaque medium. The shining through of the blood, which gives the bluish tone, which characterises the "coppery red," can only take place, where we have no opaque collagenous tissue between the plasmoma areas. Where this occurs, the colour as a whole is determined by two factors, the pure blood colour of the surface and a lesser quantity of yellowish plasmoma colour, corresponding to its depth, from which, in this case, light is still reflected outwards. Further, a great part of the transparency disappears; the colour is dull and red, with a yellowish tinge, the "raw ham" colour. The best example of this second colour is seen in the initial sclerosis, which contains the most opaque fibrillary tissue.

From this we see that both the coppery and the raw ham colour are very characteristic of the syphilide; but every clinician knows that they are now and again met with in other affections (as the coppery colour in lupus). We have there similar conditions, *e.g.*, in lupus, an increased superficial and deep vascularity. That in the healing of syphilides the commencing pigmentation may be combined with these tones, and tend more into grey, is evident, and will not for a moment be denied. But where no plasmoma is formed, as in the fresh roseola, the tinge is quite different, it is pure red, according to Fournier, even as red as a peach. Stasis—as, *e.g.*, on the papules of the legs—only adds the bluish red of the superficial capillaries, so that the coppery colour is converted into a dark mixture of brownish yellow and blue.

In addition to the polymorphism and colour, we have a third characteristic of the syphilide, *an increased consistence*, to which sufficient attention is not directed. Everywhere familiar, indeed diagnostic, is the peculiar specific hardness of the hard chancre. But all the papules, if properly felt, show a firm consistence which is common to few granulomata. There is no question, that this firm elastic character is not due to the most important constituent of the syphilide, the plasmoma as such, for then all granulomata, even the typically soft lupus, would also possess it. We find rather those elements, which give the hardness and elasticity, in the collagenous tissue, which appears most markedly in the initial scleroma, and causes its specific hardness. It is more or less peculiar to the syphilides, that the formation of the plasmoma does not hinder the simultaneous development of the fibroma. Certainly only the initial sclerosis shows both new growths, in their most intimate connection. In the papules, the fibroma is scattered in more irregular and coarse processes, and in the gumma it only forms a hard shell for the gummatous centre. The only question is, whether, in addition to the collagenous tissue, the cellular infiltration contributes to the specific firmness of the syphilide. Since the

most luxuriant plasmoma masses, such as are present in lupus, show absolutely no hardness, I think the answer must be, no. The dense collections of plasma cells in the syphilide do not contribute to its hardness, but they do to its elasticity. For, by pressure, the fibrillary elements may be pushed together, on account of the plasmoma between them, as cannot be done in fibroma and keloid; thus we have *elasticity* in the syphilitic fibroma.

There remains for notice a common character of the syphilides, which certainly contributes to make their external appearance still more irregular, that is, their *tendency to slight epithelial changes.* We find very frequently in perfectly dry papules, in which there is not the slightest trace of œdema of the cutis, certainly much more often than in the other granulomata, the lymph spaces of the epithelium dilated, the transitional layers softened, wanting in keratohyalin and widened, and the horny layer scaly. These are purely intercellular processes, which do not interfere with the consistence and power of reproduction of the epithelial cells. But the special facility with which inter-cellular œdema appears in the syphilides, explains the very different conditions of scaling which are evident on the papule, and thus we have another factor in the much talked-of polymorphism of the syphilide.

2. *Initial Sclerosis.*

The initial sclerosis is a flat or infiltrated nodule, which appears about three weeks after infection, is sharply marked off from the surroundings, and may be raised from them with (specific) facility. If the initial sclerosis develope primarily on otherwise healthy skin, there is no ulceration in the centre. The epidermis runs intact and thickened up to the border of the nodule, and only over the centre gives place to a moist, shining, beefy-red exfoliation, it is always sharply margined, round or oval, and, on the genitals, is usually the size of a pea. The form of the initial sclerosis depends on the structure of the cutis and its vessels. If this is thin and the vessels obliquely arranged, it has the form of a plate (parchment chancre), if it is thicker, that of a nodule, often with a conical extension downwards. If seated over large superficial vessels (Arteria frenuli, vena dorsalis) it may assume the form of a thickened superficial cord. Even in the typical nodular forms, the sclerosis sometimes extends as a sclerotic vascular cord $\frac{1}{2}$-2 inches long, the thickness of a quill pen, and showing the same specific hardness, most frequently following the dorsal vein. And where the cutis passes into the subcutaneous tissue (Labia majora, introitus vaginæ), the sharp margin of the nodule may be completely lost and give place to a diffuse hardening of the underlying connective tissue. If the initial sclerosis developes on the basis of a soft chancre, the induration surrounds, like a shell, a typical ulcer; but healing may occur, in the development of the initial selerosis, and then the new epidermis exfoliates, in the way typical of the initial selerosis. The secondary scleroses rarely have the sharp margining, the isolation from the healthy tissue and the specific hardness of the primary sclerosis.

After the healing of the epithelial changes and the inflammatory appearances, there remains, for a long time, a hard nodule at the seat of the initial sclerosis; indeed, in spite of its apparent complete disappearance, secondary papules and tertiary gummata may develope locally from the remains of the initial new growth (so-called recurrent chancre).

However early a primary sclerosis is extirpated, even at the first sign of specific hardness, there are always found extensive changes in the blood vessels and the epidermis, which must have taken place, unnoticed, during the incubation period. The epithelium is thickened regularly over the whole surface of the (later) nodule, particularly the prickle layer, less so the granular and horny layers. In many places only the inter-papillary ridge net is increased, in others broad epithelial masses, showing mitoses, extend into the cutis, pressing on and flattening out the papillæ. The arteries and veins of the affected vascular cone are surrounded, from the epidermis to the hypoderm, by plasma cells, their collagenous bundles are thickened, stiffer and yellower, and the fibrillary structure is less evident than normal. The endothelium of the capillaries is enlarged and shows mitosis, as do the adventitial spindle cells of the larger vessels. There exists a slight dilatation of all the blood vessels, but, in spite of numerous leucocytes in them, there is no typical emigration. Between the thickened vessels the collagenous tissue has also a coarser texture than normal and a peculiar stiffness, which is evidenced by the fact that the numerous plasma cells are almost everywhere arranged in rows, and present very regular cubical forms; they are evidently subjected to unusual pressure.

It is owing to this increased tissue pressure, to which all the constituents of the sclerosis are subjected, that, at the height of the development, the primary scleroses always present one and the same structure; in the nodules of typical hardness the greatest possible intermixture of the different constituents of the skin is reached, a maximum which, however long it last, cannot be exceeded, and only gives place to retrograde changes.

As regards the epithelium, the proliferation at the border of the sclerosis at first goes on unhindered, while in the centre, the increasing pressure of the cutis very soon arrests the further growth, and tends to flatten out the ridge net of the prickle layer. The inter-papillary ridges are once more diminished, while the papillæ swell up and reduce them gradually to sections of thin columns, which are united, like arches, over the broadened papillary apices. If the epithelium had already grown deep down before this atrophic change, its distal parts are pressed still further down by the swelling of the connective substance, compressed into fine pointed horny lamella, and may even be completely snared off from the epithelium. In those primary scleroses, in

which at the commencement greater epithelial growth took place in the centre, we may meet with some wonderfully distorted, long, thin processes of epithelium or a quantity of glittering epithelial cords, streaming radially outwards and gradually becoming lost,—or thick, sometimes completely cut off blocks of epithelium, which again enclose, in their horny crevices, small abscess-like cavities, filled by closely-packed connective tissue and wandering cells, or at least their nuclei and fragments of nuclei. In the scleroses, distinguished by great primary epithelial growth, those parts of the border of the epithelium next the centre often remain persistent as large finger-like marginal ridges, over which the equally thickened horny layer, elevated like a wall around the central exfoliation, runs. From these marginal ridges outwards, the epithelial growth rapidly diminishes. This whole marginal region of the epithelium is penetrated only by a moderate number of wandering cells, and contains few mitoses, the prickle cells are large and rich in protoplasm, the lymph spaces not strikingly dilated. Over the marginal ridge, and a little beyond it, the granular layer is usually absent, and is replaced by a broad layer of nucleated transitional cells. In the centre, on the other hand, the epithelial covering is always affected in a peculiar way by the adjacent connective tissue and its wandering cells. The mechanical change of the prickle layer has been already described, so far as concerns deep ridges and processes. But even the super-papillary prickle layer is gradually broken down by migrated wandering cells, in many places to such an extent that a finely reticulated net of compressed epithelium results, filled, like a honey-comb, with wandering cells—a dry example of the mesh-work in suppurating variola. The atrophied remains of the prickle layer are covered by a horizontal layer of compressed transitional cells closely beset with wandering cells, and therefore staining deeply with nuclear stains. Above this layer runs the basal horny layer, which remains clear with nuclear stains. The central and upper horny layers are always thrown off at the height of the process; this loss corresponds to the flat, beefy red, moist depression in the centre.

This rarefied, compressed remnant of the epithelial covering, which is beset by wandering cells, and whose firmness is shown by its preservation, overlies every true primary, initial sclerosis and clearly distinguishes it both from secondary ones and from soft sores. *The primary initial sclerosis is not an ulcer.*

The covering and the epithelium compressed inside the nodule of course aid in increasing the pressure. But in the nodule there are two different elements, whose hypertrophies dispute the ground, and finally reach a similar condition of maximal reflex penetration, such as was sketched of the epithelium and the papillary body. These are: the

collagenous tissue bundles and the plasma cells, or, to put it shortly, the fibroma and plasmoma, produced by the specific poison. In the different syphilitic new growths, both elements always appear more or less ; often, indeed, mixed up together (gumma). But they are never so closely mingled as in the primary syphilide, the initial sclerosis. While in most granulomata a certain proportion exists between the formation of plasmoma on the one hand and of fibroma on the other, and as the latter developes the plasma cells disappear (particularly in lupus), the syphilitic poison, at its point of entrance, induces a hypertrophy of all the constituents of the cutis, and thus a new formation of remarkable firmness. The plasmoma itself, however cellular it may be, can never induce any hardness. That requires hypertrophy of collagenous substance (scleroderma, rhinoscleroma, initial sclerosis), but of course, in any given quantity of increased collagenous substance, the tissue pressure will be all the more increased, the denser the cellular infiltration between the collagenous bundles.

Every section through a sclerosis at the height of development shows us that the previously perceptible sharp border of the nodule exactly corresponds with that under the microscope. From the sides and from beneath, there run towards the sclerosis, much thickened arteries, veins and lymph vessels, which, at a definite point, are no longer evident as isolated cords. This margin is marked, around the nodule, by particularly cellular vessels, in cross and oblique section, of which the latter show, by their wavy, spiral course, that the vessels have not only increased considerably in thickness, but also in length. Outside this border the finger perceives no trace of the specific hardness, and yet microscopically the sclerosed and infiltrated vascular cords run through these soft surroundings. Evidently the individual cords of the cutaneous vessels escape perception, because they lie, freely movable, in loose connective tissue. The hardness is first perceived exactly at the margin, where the individual cords are all united together by a sclerotic, cellular, infiltrated tissue.

The union is so intimate and homogeneous, that fine sections and very good staining are necessary to demonstrate the individual parts, especially the individual vessels. This is best attained by a combined elastic and nuclear stain, when the nodule resolves itself into a number of concentrically arranged, enormously widened, cross and longitudinal sections of vessels, whose character, as veins or arteries, may be recognised by a ring, relatively free from cellular infiltration, *i.e.*, the firm and broad media of the arteries. The elastic tissue is only occasionally of use in this connection, for, at the height of the nodule, it has usually completely disappeared. The comparatively small spaces between these vascular areas are occupied by regularly arranged nuclei, which surround, like a

net, the rhomboidal sections of the hypertrophic connective tissue bundles, so that sections show a certain resemblance to cross sections of inflamed tendons. The finer lymph spaces appear to have vanished, by compression; but certain large lymph spaces are all the more dilated, sheath whole vessels, nerves, &c., and split up the stiff tissue of the sclerosis, over considerable areas. The large lymph vessels, even in the firmest scleroses, also form spaces, without any sign of obliteration of the vessels.

A good protoplasm stain shows that the rows of nuclei between the connective tissue belong, almost without exception, to small cubical plasma cells. Leucocytes are very rarely met in the middle of the nodule. The absence of mitosis, in this enormous mass of rapidly developing plasma cells, appears to point to the fact that they possibly only divide amitotically, and in favour of this are the numbers of semi-segmented nuclei. The nearer one reaches the periphery of the nodule, and the less the pressure is, the larger are the plasma cells; the largest ones are directly outside the sclerosis, on the vascular cords leading from it, and on the papillary vessels of the periphery. Mast cells are present in moderate number; they are not so abundant as in the chronic syphilides. Along with the deeply stained plasma and mast cells, there appear, on the same sections, other hypertrophic connective tissue cells which, in their form, approach the ordinary cells of the cutis, in their position, do not so much form nests between the connective tissue processes, but rather accompany and sheath them and the capillaries. They are enlarged spindle cells, with several processes. They possess large, pale nuclei, and, in contrast to the plasma cells, frequently show mitosis. Their presence inside the nodule is evidently connected with the further formation of fibrillary tissue in it. In many parts of the sclerosis they form a distinct net, which the areas of plasma cells enclose and permeate, as they do the fibrillary connective tissue. Still more interesting are these cells, if we follow them beyond the margin of the sclerosis into the surrounding loose tissue. Here they are not only larger, but more varied, and thoroughly deserve the name of spider cells, since from a large protoplasmic body, which encloses one, two, or more nuclei, thick and thin processes of protoplasm run in all directions, and anastomose with the processes of similar cells. These processes are often extraordinarily thin and long, and penetrate the collagenous tissue in all directions, so that this is really permeated by a true spider's web of fine protoplasmic threads. With good methyl blue orcein stain, these fine processes are distinguished from the adjacent collagenous greenish blue fibrils by their bluish violet colour; I have never observed direct transitions between them. Further, the fibrillæ are always homogeneous, the protoplasmic pro-

cesses, like the body of the cells between, have a typical frothy structure. These partly giant "spider-cells," which are nothing more than the ordinary spindle cells of the cutis, hypertrophied outside the pressure of the sclerosis, surround the sclerosis on all sides, like a shell. They are, of course, most typically developed in the œdematous tissue around secondary scleroses (those developing on soft sores).

By the accumulation of protoplasm cells inside the sheaths of the vessels, and the swelling of the collagenous bundles, the adventitia is thickened, and the vessels show, for some distance around the sclerosis, simply adventitial changes. According as the plasmoma or the fibroma predominates, such a vessel appears, on section, either surrounded by a dense but regular layer of cells, or by a broad fibrous ring, which is penetrated, as described above, by a net-work of plasma cells. Even before the entrance of the vessels into the nodule, there is, in addition, a cellular splitting up of the media of the veins, and this takes place, later, in the arteries, usually inside the nodule. Although the intima does not share in the proliferative processes in most cases, the diameter of the vessel is considerably narrowed by the thickening of the adventitia and media, and the intima is compressed into a smaller space. In many sections, in which the seat of the vessels can be quite well recognised by the concentric arrangement of the cells and the intercellular substance, we cannot recognise one single open lumen, which shows that, during life, the sclerosis is less supplied with blood. In other cases, the lumina, though much narrowed, are still visible. Only directly under the epithelial covering, where the fibrillary hypertrophy is never so great as in the centre of the sclerosis, the capillaries, which are supplied through the collaterals, remain wide, and usually, after extirpation, are found filled with blood. From them there takes place irregular, but never considerable extravasation of leucocytes, from which those in the epithelium come.

While the fibroma and plasmoma of the vessels thus lead, in most places, to their partial or complete obliteration by pressure from without, there is frequently found, perhaps always, in some of the larger vessels, the process known by the name of endarteritis obliterans, similar, but not identical, with that which attacks the syphilitic vessels of the brain. There is always an excess of the fibroma in the adventitia, or at least in the media; the growth of the spindle cells, and with it that of the collagenous tissue, advances beyond the media inwards, and produces long swellings, which project into the lumen from different sides. On cross sections these have the appearance of three or four radially arranged conical processes, lying so close together that they almost or completely close the lumen. This is still surrounded by the swollen bodies and the nuclei of the endothelium, and

often looks like the mouth of a leech. The processes consist of fibrous tissue, containing spindle cells. The concentric arrangement, with the formation of a new elastic membrane, seen in the cerebral vessels, is never present here. Larger veins show this proliferative process of the intima just as well as the arteries; only—in view of the greater width of the lumen—the opening is never so much affected, and the swelling of the intima tissue is less, although the radial arrangement is still present. Where the plasma cell growth has reached into the media, the intima appears to remain always passive, even on the larger vessels.

If the sclerosis is formed on the base of a soft sore, we have the same changes in the tissue elements: epithelial growth, plasma and spindle cell growth, and new formation of fibrous tissue. But since the points of origin, in the one, healthy skin, in the other, the severe inflammation, the œdema and the ulcer of the soft chancre, are different, the result cannot be exactly the same. As a fact, one can always at once recognise, in an excised chancre, whether this mixed infection is present. In many cases the epithelial covering is completely absent in the centre, the walls of the ulcer are undermined, its base shows breaking down tissue, necrotic masses, and the cellular and fibromatous new growth is limited to a firm, hard shell, surrounding the true ulcer. But even if the formation of the initial sclerosis has lead to healing of the soft sore, if new formed epidermis covers the nodule, there are still indications of the different method of development. In such cases there is never such a sharp limitation of the hard nodule from the healthy surroundings, the induration of the collagenous tissue extends along the vessels, without any sharp lateral or lower margin. On the other hand, we find in many places inside the nodule, soft, loose, normal connective tissue. The cellular infiltration, too, which follows the vessels, is more areated, less equally developed through the whole nodule than in the primary sclerosis. We can see much more easily, all through the growth, the combination from individual vascular cords, for the transformation of the inter-substance is not complete. These differences are evidently the results of the fact that the tissue was in a high degree œdematous, before the cellular new growth and the fibrillary hypertrophy ensued. And, for the same reasons, the lateral pressure of the elements in this nodule is less; the vessels possess, in spite of marked adventitial growth, a normal, or even an excessive width, the lumina, the lymph vessels and plasma cells have, in the centre of the nodule, apparently the same size as at the periphery, the reticular appearance of the compressed cells and collagenous bundles is not found throughout, but only at parts of the nodule. Finally, certain symptoms in the neighbourhood of the nodule

point to the presence of soft chancre; there are many wandering cells in the neighbouring epithelium, and œdema of the surrounding cutis, which is particularly rich in large plasma and spider cells.

I cannot doubt that the uncertainty as to the histological nature of soft chancre on the one hand, and initial sclerosis on the other, depends mainly on the fact, that such mixed chancres have been regarded as typical of initial sclerosis. For the study of the latter, only pure, primary, simple, hard, well-defined nodules should be examined. The *very hardest* scleroses are, on account of their hardness, naturally the best, and, where the hardness is extremely developed clinically, it will be found that the formation of plasmoma is very slight, compared to that of fibroma.

It is a frequent observation that, after an anti-syphilitic course and long healing of the initial sclerosis, there is still present a firm, indolent nodule of lesser size, which may remain for years recognisable. I had the opportunity of examining such a nodule immediately after the course, and will give my results, because on the one hand it shows the basis on which the so-called recurring chancres develope, *i.e.*, secondary and tertiary syphilides at the seat of the initial sclerosis, and on the other hand it indicates the manner of the absorption of the latter.

The nodule in question was of the size of a pea, and was microscopically as well defined as it felt; it was in the centre of the cutis. The cutis which covered it was formed of normal, soft, collagenous tissue, in which ran greatly dilated blood and lymph vessels, and in which a net of fine elastic fibres had re-formed. The connective tissue cells, running through the tissue, were hypertrophic but usually of simple spindle form. Plasma cells were only found singly, scattered in the connective tissue, but were very abundant along the dilated capillaries of the superficial vascular net. The epidermis, thickened as a whole, showed numerous mitoses. In distinction to this, almost normal, upper part of the skin, the nodule lying beneath was formed of a dense felt-work of cells and collagenous tissue, which in many places still showed its composition from widening cords, but in which no lumina or vessels were evident. But there had evidently taken place a new arrangement of the densely-packed cellular masses into roundish or oval areas, very rich in small and large giant cells. Giant cells are certainly found in all the more chronic syphilides, but in the initial sclerosis, at the height of development, I have never observed them. Here, in the slowly-disappearing remains of one, they are almost as abundant as in lupus. As there, they arise from paled plasma cells, apparently not from a want of cell division after nuclear division, but from the coalescence of such multi-nuclear groups of cells.

There are found indeed many foci of mono- and multi-nuclear cells, whose protoplasm already presents, here and there, the finely reticular, cloudy appearance of perfect giant cells, but they only partly hang together by their protoplasm, or are simply fitted into each other. In fact, this is an excellent object on which to study the sub-acute formation of giant cells. In spite of the many giant cell areas, the appearance of the whole nodule was not "lupoid," for there was present the close interweaving of cellular fibrous tissue and newly-formed vascular capillaries; while lymph vessels and elastic tissue could not be recognised in the nodule. Altogether then we have, as in the initial sclerosis, an equal formation and intermixture of the syphilitic plasmoma and fibroma, no longer, however, closely dependent on the pre-existing blood vessels, but around individual centres of proliferation, and the formation of strikingly numerous giant cells, along with intermediary new formation of blood vessels.

This leads on to the description of the structure of an initial sclerosis, left to itself for eight years, which I published many years ago. Here there were a number of miliary areas, completely caseated in the centre and containing giant cells, lying in a richly vascular, otherwise normal cutis, only a few of which could be related to pre-existing vessels; most of them appeared to have been formed independently inside their adventitiæ.

The histology of the vascular cord (not so well named lymphatic cord) which is present in many scleroses, is exactly the same as that of the sclerosis itself—a plasmoma and fibroma of the blood vessels and their sheaths, in which the unaffected lymph vessel is passively included.

3. *Secondary Syphilides.*

Roseola.

The roseola, the first symptom of generalisation of the disease which appears in the skin, is evident six or seven weeks after the appearance of the initial sclerosis, ten weeks after the infection, mainly on the sides of the trunk; only when long left alone, on the extremities and head. It has the form of fresh red spots, the size of a lentil to a bean, which are usually oval and irregular, always distinct and not elevated. The eruption appears slowly, usually unnoticed, and reaches its height in eight to fourteen days, new spots daily appearing between the old. Then the hyperæmia of the spots diminishes, they become grey and disappear without desquamation. There is no tendency to the formation of groups of rings. In severe untreated cases they may pass directly into papules. Now and again they are somewhat œdematous, but do not acquire a white centre, nor do they itch (Roseola urticata), sometimes half-a-dozen or more hair follicles appear on their surface [Roseola granulata, a variety which may appear locally or generally (Besnier), even without hyperæmia (cutis anserina, roseoliformis)]. The "tardive" and circinate syphilitic roseolæ belong to the neuro-syphilides.

While clinically roseola appears to be a perfectly superficial erythema, we find, histologically, changes, though only of a slight nature, in all the layers of the cutis, from the sweat glands outwards. Not only are all the blood vessels of the superficial and deep net widened, but they show enlargement and multiplication of the peri- and endothelium. Even the cells scattered in the cutis are enlarged, especially around those coil glands whose epithelium shares in the enlargement. We find the protoplasm of the coil epithelium mostly swollen, all the nuclei pressed towards the lumen, sometimes the lumen even dilated, and the cells irregularly projected into it. Plasma cells are not yet present, nor is there any increase of leucocytes in the tissue. The epidermis shows no abnormality.

We find more important changes in the more inflammatory *Roseola urticata.* Here, with the inflammatory œdema, numerous leucocytes pass into the spaces of the adventitia of the vessels, then into the cutis tissue, and, finally, into the epidermis also. The lymph spaces of the cutis and the epidermis are distinctly dilated. The dilated canals in the latter, appear, with a powerful protoplasm stain, as a clear net, running all through the prickle layer, and containing a moderate number of leucocytes. In this we see already that yielding of the epithelium to the syphilitic exudation, which is common to all syphilides. Other changes are those of Roseola simplex.

The process extends in another direction in *Roscola granulata.* This variety forms a transition to the papule, the typical form of the secondary syphilide. There are now found, in addition to the symptoms of vascular dilatation and simple cellular hyperplasia along the vessels, here and there, *areated collections* of large cells, with all the characters of plasma cells. These areas develope around the vessels, especially those supplying the coil glands, so that these are embedded in a collection of plasma cells. They are found also in the immediate neighbourhood of the hair follicle, and accompanying the blood vessels up to the upper vascular net, but they only occasionally send processes into the papillary body. We have here then, already, a cellular new growth, a granuloma of moderate size following the vessels like a cord, which, in some places—as around the coil glands and the follicles—swells up in the form of nodes, and, partly from this, partly apparently from an irritation of the oblique cutaneous muscles (which are not permeated by the new growth) gives to the surface of the skin the fine granulated appearance. The structure of these areas is the same "*en detail,*" as that of the syphilitic papule "*en gros.*" The external cells are large, cubical, deeply-stained plasma cells; then come, towards the inside, paler, but still large, indeed swollen, multi-nuclear plasma cells, mixed with small mono-nuclear ones, and here and there appear, in

the centre of these areas, a few pale multi-nuclear giant cells. The tissue between the plasma cells is partly normal, partly atrophic, never hypertrophic. To these, everywhere present, important constituents, there are added, in varying but never great numbers, ordinary fine spindle cells and leucocytes. The latter are never arranged in groups or layers in the areas, but are always single and irregular, as are the very scanty mast cells. From the commencement of the new growth in lupus, these areas of plasma cells are distinguished, by the looser, more irregular formation and the enclosure of normal collagenous tissue. The elastic tissue in them has disappeared.

The Papule.

The basis of all secondary syphilides is the papule, a firm infiltration of the cutis projecting over the surface of the skin, of a fleshy red or coppery colour, and with a smooth, dry surface at the commencement of its development; later, it takes a more livid colour, readily scales, and finally heals without a scar; through the whole of its course it gives rise to no subjective symptoms. Of this main type there are two varieties, the *small papular* and the *large papular* syphilide, which are distinguished by the lesser or greater extension of the cellular infiltration. Then there are two different categories of variations of the main type,—(a) variations induced by *special local conditions*; (b) variations induced by the simultaneous existence of the other cutaneous affections, which partly favour, partly modify the process of the syphilitic new growth—*mixed infections.*

(a). *Local Varieties.*

To this belong the moist and eroded papules of the contact areas and mucous orifices, caused by excessive external saturation of the epithelium. Where the orifices are sometimes stretched and sometimes narrowed, as at the angles of the mouth and at the anus, there appear radial folds on the papule (papulæ radiatæ). In their fullest development, the papules growing at the contact areas take the type of broad condylomata (papulæ condylomatosæ). Where, on the other hand, the epithelium is excessively dry and callous, as on the palm and sole, the papules are flat, livid, and very hard from epithelial thickening (papulæ palmares et plantares), or there is a bullous elevation of the horny layer (syphilis bullosa neonatorum).

(b). *Mixed forms between Syphilis and other Dermatoses.*

These are excessively numerous, embracing a great number of the so-called simple syphilides. They induce, still more than the occasionally different appearance of the individual eruptions, the well-known and diagnostically important polymorphism of the syphilide,

for the accompanying dermatoses do not mark all, but only those syphilitic eruptions suiting their special topography, with their particular stamp. In general, it is only the *inflammatory* affections of the skin which show this connection with the syphilides, for we know that all the syphilides are preferentially localised on artificially hyperæmic areas.

Various follicular hyperæmias (Eczema folliculare, Keratosis follicularis), which chiefly affect the back, the buttocks, and the extensor sides of the extremities, lead, in addition to small or large syphilides of other parts of the skin, to a very widespread eruption of tiny scaling papules, localised at the mouths of the follicles of the affected regions, which are the smallest produced by syphilis (Syphilis follicularum, Syphilis punctata).

In distinction to this rare form is the commonest combination, almost as common as the uncomplicated syphilide, that with all the forms of *seborrhœic eczema.* With it I reckon the small papular, scaling, early eruption of the scalp (S. papulo-squamosa or papulo-crustosa capitis), the coarse papular "Corona veneris" at the margin of the forehead (S. papulosa marginalis frontis), the coarse papular, confluent syphilitic rosacea of the centre of the face, accompanied by Rosacea seborrhoica (S. papulo-crustosa naso-labio-mentalis), the serpiginous scabbed syphilide of the palm and of the sole, which some separate from the simple syphilides as S. palmaris (S. papulo-crustosa palmaris et plantaris), and all those large papular syphilides, which often itch, extend serpiginously on the trunk and head, and are accompanied by crust formation, which are included under the names: psoriatiform, papulo-crusted, circinate, and papulo-serpiginous syphilides (S. papulo-crustosa circinata).

One would expect that the combinations with ordinary suppuration would be at least as frequent as the combination with seborrhœic catarrh, and that the white and golden pyococci would be often met in secondary syphilis, with or without suppuration. But this is, as special investigations have taught me, certainly not the case. In fact, secondary suppuration of these syphilides under the influence of staphylococci is so extremely rare, that one may almost speak of an immunity of the syphilitic papule to suppuration. Certainly no one has examined any of the pustular syphilides in this connection, and possibly the so-called acneiform syphilide, which I have not been able to examine, may prove to be a mixed infection (S. pustulosa acneiformis). Of the other forms, however, the so-called varicelliform, varioliform and ecthymatous syphilide, I can state, from my own investigations, that no mixed infection with ordinary pyococci is present, indeed it is questionable whether there is a mixed infection with any

kind of pyophoric organism. Not wishing to trespass on future investigation, I leave for the present the *varieelliform* and *varioliform* syphilide in the group along with the *ecthymatous*, whose mixed origin is the most likely.

This appears, usually in reduced individuals, but also in perfectly healthy ones, in the form of large circular and oval pustules, which throughout resemble non-syphilitic, infectious *ecthyma* (and *rupia*) and is most probably to be regarded as a mixed infection of the poisons of these diseases and the large papular syphilide. They differ from one another, in that the ecthyma crusts are finer, more simply constructed and easily elevated, the rupia crusts are arranged like limpet shells, sometimes rounded to a conical point, and very adherent; still this difference perhaps depends only on the subsequent peripheral extension of the ulcerating process in rupia, a circumstance which is also in favour of a mixed infection. Syphilis papulosa ecthymatosa and rupioides usually leave scars.

Still more uncertain, and dependent altogether on future investigation, is the position of the so-called corymbose syphilide, in which a group of daughter papules form round a mother papule, and of the vesicular syphilides in which—certainly only transiently—the formation of vesicles has taken place at the apex of the papule; both of them conditions which are not proper to the syphilitic papule. At most, the vesicle formation may be regarded as a distant analogy of the bullous syphilide of infants. The cockade-formed syphilide, deeply pigmented in the centre or at the periphery, belongs to the neuro-syphilides.

We have consequently to describe, as the most important representatives of the secondary syphilides:

I.—*The simple papular syphilides.*

(a). The small papular syphilide;
(b). The large papular syphilide and its varieties—
  (α). The condylomatous papule,
  (β). The palmar papule,
  (γ). The bullous papule of infants;
and in conclusion,
(c). The healing of the syphilitic papule.

II.—*The mixed papular syphilides.*

(a). The papulo-crusted syphilide.
(b). The papulo-crusto-pustular syphilide. (Ecthyma.)
(c). The varicelliform syphilide.
(d). The varioliform syphilide.

I.—*Simple papular syphilides.*

(a). *The small papular syphilide.*

The cellular infiltration, the size of a peppercorn to a pea, which is the important constituent of this syphilitic papule, extends over an area having a diameter of about ten or twenty papillæ, and reaches in the centre as far down as the middle of the cutis, while, at the periphery, it is simply a thickening of the papillary body. It thus presents as a whole the form of a lens, with the upper surface flatter, and the under more convex, being lengthened out towards the hypoderm in the direction of one or more blood vessels. The epidermis above it, is, unlike the condition in initial sclerosis, not affected in the process, but is only flattened by pressure, often the ridges have entirely disappeared. Only when the condition has lasted long do we find a few leucocytes and mitoses in the epithelium.

If we follow the growth, from the healthy tissue of the periphery towards the centre, we find at first a few plasma cells around the capillaries of the superficial vessels, as well as swollen endo- and perithelium. Then come capillaries, which are surrounded by plasma cells, then one or two papillæ, which are almost filled with deeply-stained large plasma cells, and finally, the broad plasmoma filling the papillæ and flattening the ridges. Examined from below upwards, we find, first on the arteries, and still more on the veins, a thin mantle of plasma cells, which gradually thickens until about the middle of the cutis, where it joins the nodule. Inside the nodule it is best to commence with the wide lymph vessels and spaces, and to proceed outwards from them. These are not surrounded by plasma cells, but by a small homogeneous border of connective tissue, and are lined by simply swollen, not otherwise altered endothelium. The spaces surround rounded, irregular islands of tissue, which are richer in plasma and hypertrophic spindle cells in the centre than at the periphery, and show, more or less distinctly, either in the centre or towards one side, a compressed capillary or even a large blood vessel.

The plasma cells of the periphery, of the extensions of the nodule along the peripheral vessels running into it, and of the immediate neighbourhood of these vessels inside the nodule, are large and stain deeply. All the other parts of the nodule show only a few plasma cells, among densely compressed, less stained, smaller and larger (multinuclear) connective tissue cells, and, pretty regularly, in the centre of large groups, giant cells. The fully developed large giant cells show no important differences from the giant cells of lupus. They contain, in addition to a round, elongated or branched, finely reticular, cloudy mass

of protoplasm, a number of nuclei, arranged as a horse-shoe, or collected at one pole. But in the quantity of incomplete giant cells, which the papule contains, and which corresponds to the more acute development of this formation, we recognise the non-existence of tuberculosis. As such I regard the appearances, everywhere visible, in which the protoplasm of small multi-nuclear plasma cells resembles that of giant cells, while close by, other small plasma cells show four, six, or more nuclei, with lesser remains of protoplasm ; and there are yet others, completely homogenised, scarcely showing the nucleus. We have here all the parts of a larger giant cell close together, and the adjacent position of the cells usually indicates the position of the future nuclear mantle and the homogenised mass of protoplasm. Considering that we sometimes find here, as in lupus, complete small cells, with the nucleus alone well stained, enclosed in larger giant cells, we can hardly avoid assuming a development of large giant cells from the coalescence of smaller multi-nuclear cells, the *specially homogenised cells* being surrounded by those in which the nuclei still retain the power of amitotic division. We can at least better study the genesis of giant cells here, than on the much more chronic tuberculosis of the skin.

A further difference from a small nodular lupus, consists in the lesser number of small plasma cells, daughter plasma cells, which share the staining reactions of the larger ones, but only have a small ring of protoplasm. In lupus, these are found in flocks, or rather in layers, passing into the homogenised centre of the lupus, so that, on account of their dimensions and numbers, they have almost always been regarded as leucocytes. In the syphilitic papule this form plays a much less important rôle ; the large plasma cells usually pass directly into the central homogenised cells.

I find a third distinction from the tuberculous condition, in the larger amount of ordinary spindle cells and remains of fibrillary tissue, which are preserved along the lymphatics in the syphilitic growth. It is this condition to which the areated appearance of a syphilitic papule is due on section, and which prevents it from having the appearance of a smooth mosaic of cells. Even at the height of development, we can trace its origin from a cord-like plasmoma, originally surrounding the vessels, for the processes which unite to form the nodule are always arrested in their proliferation at the larger lymphatics.

The uncomplicated papule hardly contains any other constituents, in particular very few mast cells and leucocytes. There are no mitoses.

The small papular syphilide is certainly not limited to any one constituent of the skin ; there are no doubt cases in which the infiltration is localised with considerable regularity, both clinically and histologically, around the follicles ; it may be that there is a congenital

idiosyncrasy of the perifollicular vessels, or more probably some additional external irritation. This localisation makes no difference in the nature of the papule; the plasmoma is only arranged, like a shell, around the follicle and its surroundings, and therefore less extended laterally, and the whole papule assumes an acuminate form, with the swollen follicle as its centre. This form has been called Lichen

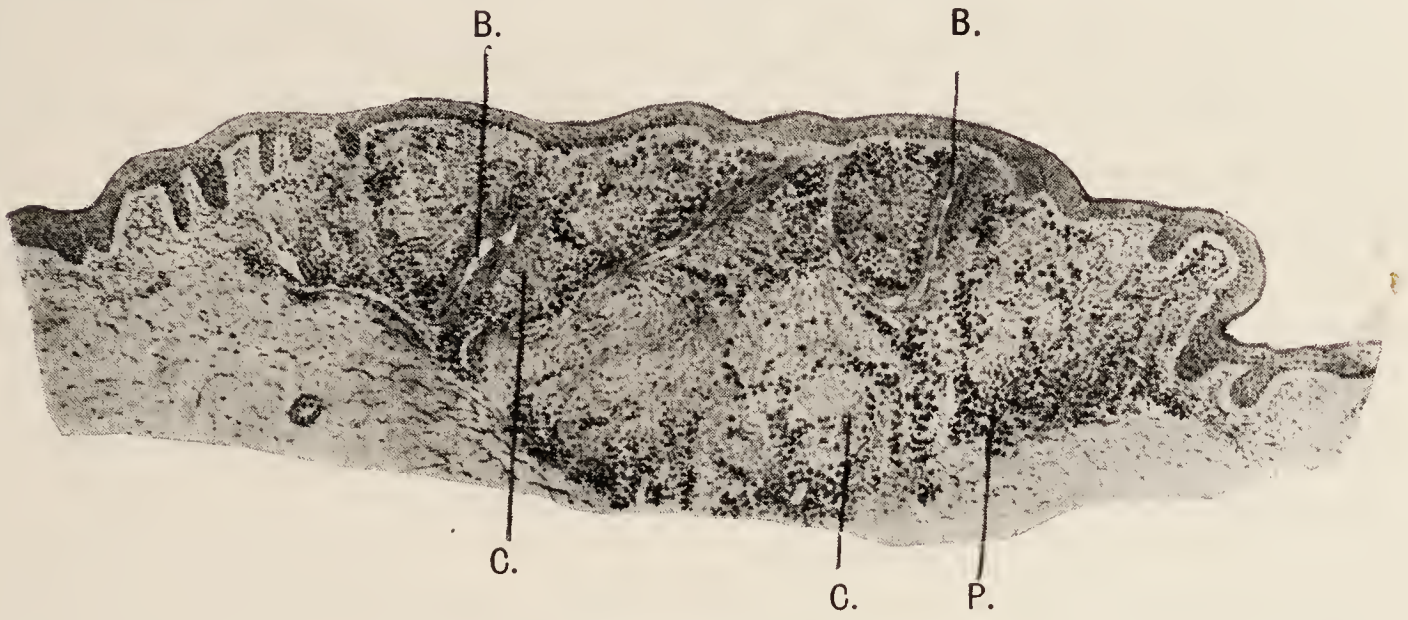

FIG. 22.—Syphilitic papule.

C. Pale cells surrounded by *P.* plasma cells. *B.* Blood vessels.

syphiliticus; it of course possesses not the slightest histological resemblance to the papule of Lichen planus; rather, on account of the invariable presence of giant cells, to the so-called Lichen scrophulosorum. The name "miliary syphilide," which many authors give to the small papular follicular form, is also unjustified, for the shell-like infiltration, flattened out, corresponds to the ordinary size of the small papular form, and the two are histologically related, for their structure is the same and their limitation from the surroundings sharp, so that, even when present in great numbers, they do not run together. This last peculiarity separates them, even histologically, from the large papular syphilide.

(b). *The large papular Syphilide.*

While the small papular syphilide represents the ordinary type of the early, universal, profuse secondary syphilides, the large papular form is the type of the more solitary recurrent papules which appear in lesser numbers, later. They are of the size of a lentil to that of a shilling, or larger; have a flatter surface, and a less sharp limitation in breadth and depth than the small papular syphilide, cannot therefore be so well isolated from the surroundings, and give, as a whole, the impression of denser infiltration. They are usually of long duration, and by coalescence give origin to flat infiltrations.

The histological formation of the large papular syphilide is in the main the same as that of the small; we have a new formation of plasma cells, especially in the upper part of the cutis, which is at first strikingly limited to the vessels, but later affects the cutis between. We have, therefore, only to note the points of difference from that form. The plasmoma here is less compact, the islands, containing free collagenous tissue, simple cells, here and there even elastic tissue, but always large, gaping lymph vessels and spaces, occupy a much greater space than in the small papular syphilide. The histological appearance is therefore not so strikingly that of a uniform nodule; the large papular form is, however, more like the small papular than the diffuse form of lupus is like the nodular. But the analogy goes no further. The amount of homogenised plasma cells and giant cells varies very much in different papules, but most of them consist of deeply stained, large cubical cells, and the extension of the degenerative processes in them by no means corresponds to the extension of the cellular infiltration as a whole. We find, in every section of older papules, half a dozen or more giant cells, quite irregularly arranged, sometimes in the papillary body, sometimes at the under margin of the infiltration.

In older, long-standing, large papular syphilides the epithelium often shows changes, but never extensive ones. In some places, especially where hair follicles run through the infiltration, there are formed, by these circumscribed growths, apparent epithelial giant cells, in which nuclear division is more rapid than that of the cell. In other places the epithelium is permeated by wandering cells, but this does not lead to suppuration or the formation of vesicles. It is, I think, questionable whether this inconstant leucocytosis is not to be regarded as a sign of some other complicating inflammation. At such places, the lymph spaces of the epithelium tend to be dilated, and there is, as a result, a fine leafy scaling, which leads to epithelial mitosis. Equally unimportant and accidental is the collection of mast cells in certain spots; in general they are sparing, and only a little more frequent than in the small papular syphilide, because the condition lasts longer.

(α). *The condylomatous Papule.*

The so-called "broad condyloma" is only a very common variety of the large papular syphilide. All that is necessary is a persistent soaking of the epithelium and a certain degree of hyperæmia, such as is supplied at the contact areas and the mucous orifices. The constant rubbing and the greater warmth of these regions favours the condylomatous development of the papule.

Histologically, this modification is characterised by great growth of the epithelium, distinct dilatation of the vessels, œdema of the

cutis, and, what is otherwise not common to the papule, profuse emigration of leucocytes. The acanthosis, in particular, completely alters the appearances, for the deeply penetrating epithelial ridges take up almost the whole new formation of plasma cells between them (*i.e.*, in the newly furrowed-out long papillæ), so that only a small zone of infiltration remains under the epithelial margin. The original connective tissue growth thus attains almost the appearance of an acanthoma, and the old conjunction of it with the so-called (acuminate) condyloma is, when superficially considered, justified even histologically. But closer investigation soon shows that the nucleus of this new growth is a plasmoma, extending along the much dilated vessels. Neither the homogenised plasma cells nor the giant cells are absent, and the latter are hardly less numerous than in the simple papule.

The lymphatics occupy a very large space of the connective tissue, which is already limited by the epithelium; large elongated papillæ, often swollen into knobs at their ends, carry, in addition to the dilated capillaries, a wide, gaping lymphatic. Where the epithelial ridges are closely arranged, the plasmoma in the papillæ is consequently limited to the small zone between the dilated blood and lymph capillaries. But the epithelial growth takes place irregularly, and wherever the epithelial ridges have not penetrated (could not penetrate), the whole space is occupied by a dense mass of large plasma cells. At such places the condylomatous papule is only distinguished from the simple, by its wider vessels and greater œdema. The profuse emigration of leucocytes above referred to is limited especially to the apex of the papillæ, even if it is everywhere recognisable. Mast cells are present in moderate number.

The epithelial growth, the most striking symptom of this variety, is, in contrast to (acuminate) condyloma, almost exclusively inter-papillary. The supra-papillary prickle layer, squeezed between the horny layer and the dilated capillaries, is rather thinned than thickened, especially at the height of the development, if the growing epithelium has found an outlet in the deep, penetrating ridges. The ridges are regularly formed, sometimes broad, sometimes small, and have multiform, usually very thin processes, which dig out, between them, secondary, smaller papillæ. The prickle cells which compose them are larger than normal, the older ones are often œdematous, the younger ones show mitosis. The whole prickle layer is penetrated by dilated lymph spaces, and a varying amount of leucocytes. The latter, here and there, form, especially above the papillary apices, an almost complete net, which fills the lymph spaces of the thin supra-papillary prickle layer, up to the horny layer. But other parts of the prickle layer, especially the under parts of the ridges, are almost completely free from wandering cells. Here

also, one sometimes sees incomplete epithelial division, which has led to the formation of small epithelial giant cells, and epithelial plugs, which fill the lumina of the coil ducts. The hair follicles, which run through the papule, often share in the epithelial growth. The surface of the condylomatous papule consists, according as it is clinically dry or moist, of true horny layer, moist scales, or even purulent crusts. In the former case, there succeeds to the prickle layer a well-developed granular layer, which is depressed over all the broad ridges, and is there thickened to three or four layers, while over the papillæ it runs in a simple layer. The horny layer is more or less thickened, especially over broad epithelial ridges. But where the œdema of the prickle layer is very marked, the granular layer tends to be replaced by a transitional layer, with rod-shaped nuclei, and without kerato-hyalin, which, like the horny layer above, is permeated by leucocytes. Where the leucocytosis is greater, the prickle layer is transformed, by simple drying, into a purulent epithelial crust, which, when it falls off, leaves an eroded surface, coloured white by swollen epithelium, and readily bleeding, owing to the position of the papillæ. In this crust we always find a quantity of bacteria, among which cultivation shows the organisms both of suppuration and of putrefaction. It is exceedingly probable that these are the cause of the suppuration, which is here a pretty constant symptom of the syphilitic papule. For suppuration is not a character of the simple papule, it is often absent, even here, in the dry condylomata, and is mostly only developed in places, not in the centre of the condylomatous papule, but near the surface. To ascribe the condylomatous transformation to these secondary organisms of the contact regions, is a tempting, but as yet unproven hypothesis.

(β). *The palmar and plantar Papule.*

The papule which is localised on the palms and soles shows a certain analogy to the condylomatous papule, in so far as the plasmoma is drawn, by the simultaneous growth of the epithelial ridges, into the elongated papillæ, and, as a uniform lenticular new growth of the cutis, almost disappears. Thus the papule at the first glance resembles the parakeratoses, but we have the important infiltration of plasma cells, which is not present there. This, in a thin layer, fills the papillæ, extends along the blood vessels as far down as the coil glands, and surrounds them in the form of rounded areas. The blood and lymph vessels are also dilated, but in nothing like the same degree as in the condylomatous papule. The emigration of leucocytes is minimal. The intra-papillary prickle layer is increased into long folds

by the mitotic division of the prickle cells, the supra-papillary layer may be even diminished, while a thick granular and horny layer lies over it. In many places, where the horny layer shows callous thickenings, the granular layer has completely or partly disappeared, and is replaced by a flat, nucleated, transitional layer, in which scattered foci of leucocytes are found.

(γ). *The bullous Papule of infants.*

The only papules which show a tendency to bullous elevation of the horny layer are found in the hereditary syphilis of infants, typically, on the soles and palms, but also on other parts of the body with a resistant horny layer. The papule which forms their base, shows important differences from that of the acquired syphilis of adults, so that, histologically, the bullous formation is by no means the most striking peculiarity. There are no plasma and giant cells, while the number and size of the spindle cells, along the vessels and in the papillary body, is certainly greater than normal. In this the papule of infants resembles the simple roseola of adults, and in addition it shows marked leucocytosis. The epithelium shows the same changes as in adults, no tendency to vesicle formation from colliquation, but, on the contrary, to dilatation of the inter-epithelial lymph spaces, and this extends so far in the papules of infants, that, above the cellular infiltration of the cutis, the epidermis is penetrated by many large and small inter-epithelial spaces, containing a quantity of closely-packed wandering cells. Only occasionally does the epithelium at the margin of these areas soften. The bulla does not develope by the confluence of the spaces of the prickle layer, but by the elevation of the horny layer from the mechanically altered prickle layer, whose epithelial spaces, so far as they lie superficially, ultimately open into the large monolocular exfoliative bulla. Where the horny layer is less thick than on the soles and palms, the sero-purulent exudation directly reaches the surface, which then becomes moist or covered with crusts, as in the broad condyloma or the papule of eczema.

(c). The healing of the Papule.

The *healing of the syphilitic* papule is of interest in more than one direction. Not only is it of the greatest practical importance to know how much of a syphilide remains when it is clinically considered healed, but we will be able to conclude, from the order in which the histological appearances disappear, what were their relations, and, from the manner in which they disappear, how they have developed. A universal papular eruption, which had developed without any treatment,

and which was examined weekly during treatment with mercurial inunction, clearly demonstrated the regressive metamorphosis of this papule.

The untreated papules showed all the conditions, described above of the simple small papular syphilide, so exactly, that they might have served for that description.

The papules of the second series were, clinically, completely flattened out, but could still be recognised as small, firm, brownish red enclosures, of the original size. It is first evident, that the diminution of the infiltration is completely concentric; it reaches, here also, from the cutis to the sub-papillary vascular net, but the area itself, in view of the flattening of the nodule, is smaller, about half its original size. It is remarkable that the atrophy does not affect the deeply-staining plasma cells. These, if not increased, are, even in the smallest nodules, at least as numerous as before. With a good protoplasmic stain, the whole nodule stands out even better than at the acme of the process, because the same number of plasma cells is compressed into a smaller space. Further, the plasma cells and the clear homogeneous cells are now more regularly distributed than was previously the case, very much as they are in the lupus nodule. The former usually surround the latter concentrically, so that sections, under a low power, appear to be composed of round individual foci. In addition to this polycyclical appearance, the infiltration, in the narrowing or disappearance of the blood vessels and the swelling of the spindle cells and collagenous tissue in the centre of the foci, strikingly resembles areated lupus. Only in this stage of absorption, is it possible to confuse the syphilitic with the lupus infiltration.

As regards the individual constituents of the papule, all of them, with the exception of the giant cells, show striking changes. In these latter only the nuclei are less stained; the circumference, and the appearance of the protoplasm are hardly altered. The deeply-stained, large plasma cells, on the contrary, show, in the middle of their darkly granular protoplasm, clear, unstained, rounded spots, vacuoles, at first singly, then in groups, until the cell presents the plasma granulation only in parts, usually at one pole. These plasma cells, which have been partly robbed of their chromophilic protoplasm, have a finely vesicular, frothy structure, like the ordinary connective tissue spindle cells. Where the chromophilic substance goes to is plain enough, for there are always found, in the neighbourhood of these cells, irregularly formed globules and angular fragments of the same colour, sometimes still hanging on to the clear plasma cells.

The pale, usually multi-nuclear cells are arranged more closely than previously in the central part of the rounded area (like lupus) and their nuclei are paler than normal. Some show here and there

greyish blue granules at one end or at the border, sometimes in finely reticular form.

These changes are still more striking in a papule of a third series, which had sunk below the level of the skin, and looked partly yellowish, partly greyish-blue. The infiltration here is, along with the affected area of skin, diminished and flattened, but it is still much more prominent than one would expect from the clinical appearance. The regular concentric areas, which recall the appearance of lupus, are here less prominent, the papule is again more loosely formed, and this, as is seen at a glance, is owing to a striking numerical diminution in the stained plasma cells. Closer examination shows that the process of throwing off chromatophilic substance from them is in full cry. Thus the cells show the most remarkable forms, sometimes tail-like processes, which break off, sometimes cup-like separation of whole parts of the cell, which later break down, sometimes snared off parts, showing mulberry-formed or rosette-like clear vesicles, and between them broken off, stained particles. The region between these cells swarms with deeply and faintly stained masses of the most varied form and size down to the finest coloured globules, and these are carried by the lymph stream into the lymph spaces of the epidermis, which, here and there, are filled with them. In addition to these more or less deeply-stained fragments, there are also found unstained vesicular globules, which, with a plasma cell stain, show only a slight greenish shimmer, and lie free in the tissue, either singly or in groups. By the adherent chromatophilic granules, which still have the bluish-violet colour of the original plasma cells, they may be identified, and are no doubt to be regarded as the vacuolated remains of the cell protoplasm. We see similar appearances in the clear multi-nuclear cells, which have taken up a still more chromophilic substance, and show at certain places a spongy structure, with reticularly arranged, bluish-green granules between the vesicles. That these vesicles could have been taken up as a whole into the homogeneous cells from those lying free in the lymph spaces, is improbable. The cells have evidently only taken up stainable substance from the lymph, and this has extended in them in a reticular fashion.

I would not have given such a thorough description of these vesicles, laden with stainable substance, and the stainable fragments themselves, had they not been liable to be confused with pigment, a substance everyone would certainly expect in those dark-coloured, healing syphilides, but which I have diligently sought for in vain. The ashy-grey colour of the remains has no more to do with pigment than the coppery colour of the earlier syphilide. If we examine sections unstained, or only stained with a nuclear stain, we see no

trace of these fragments and vesicles; they are only evident when more or less deeply stained with a protoplasm stain. But even the ordinary golden pigment of the cutis is as rare as the normal brown pigment of the epidermis. Pigment in the cutis, I have found, now and again, in healing papules, but only in limited spots, and therefore without any relation to the dark grey colour. Epidermic pigment, is, at this stage, almost completely absent. I think it is beyond doubt that the inflammatory process leads to the destruction of the normal pigment, and that the healing papule, paradoxical as it may sound, is in general poorer in pigment than the normal skin. So much is certain, that the pigmentation of syphilis, whether it developes alone or as a result of other syphilides, is to be regarded as a *process "sui generis,"* and not as a necessary result. The explanation of the ashy-grey colour of these remains is supplied when they are examined with the diascope. Then the grey spot is converted into a faint brownish-yellow one, which represents the remainder of the plasmoma. Since the blood from beneath still shines through, and the superficial capillaries are no longer dilated, a greyish-blue tone is mingled with the brownish one, and causes a blackish-grey colour.

In relation to the mast cells, also, the papules at this stage of healing show peculiar changes. We find, with methyl-blue orcein stain, a number of spindle or elliptical cells, which only partly, *e.g.*, on one side, show the metachromatic red granulation tinge, a sort of semi-mast cells. Other connective tissue cells of the ordinary type show single granules; others, again, in addition to that, a diffuse metachromatic reddish colour; and finally, there are also mast cells, which are closely beset with granules, and show in addition this diffuse colouring. It must be noted that these finer changes are only evident when using the above method, not with the ordinary acid decolorisation. Is this, then, a formation of new mast cells, or some peculiar variety of them? I incline to the first explanation, in favour of which is the form of those cells which only show partial mast-cell granulation, which does not differ from that of the ordinary connective tissue cells, then the circumstance that these formations appear, and are more numerous inside the breaking-down plasmoma than the complete mast-cells were inside the fully-developed papule, and, finally, the diffuse metachromism of some, which may very well represent the lye from which the later granulation is deposited. Around the healing papule there is further found a quantity of very large, queerly-shaped, ordinary mast cells, which leave in their trail numerous free granules.

The fourth series of papules comes from the period of healing, when the patient was discharged as temporarily cured. Most of the papules were converted into greyish-yellow, just visible spots; others,

again were sunk somewhat beneath the surrounding level. These showed quite a remarkable infiltration of the cutis with plasma cells; the process of breaking off of chromatophilic substance by no means leads to the disappearance of the whole plasmoma; part remains, perhaps long. While the production of the stainable substance appears to have been arrested for the present, the clear cells have taken it up in greater amount, and even the giant cells are laden with it. In the latter the blue granules are distributed in their finest form through the whole cell body, which shows, in passing, that the giant cells are living cells. In the pale, mostly multi-nuclear cells, the substance is found collected in coarser granules, singly, grouped reticularly, or at the periphery of intercellular vacuoles. Both varieties of cells now take a light, diffuse, greyish-violet, basic protoplasm stain, which they did not in the earlier papule. Just as here, one sees in the epidermis an active importation of chromophilic substance, the basal and adjacent intercellular spaces being partly or completely filled with it, and thus we get the appearances of branched cells, as in many true pigmentations. These, accidentally showing with basic stain, may have imposed upon some as pigment; but unstained sections show nothing of these intercellular masses. Nevertheless, this very distinct process is not without value, as an analogy, in explaining the true pigmentations of the cutis and epidermis.

In addition to these events, we have now a rarefaction of the connective tissue, inside the plasmomatic area, which is already prepared for, at the height of the papule, by the disappearance of the collagenous tissue in proportion to the growth of the plasma cells, but is now first manifest with the partial disappearance of the plasmoma. The lymph spaces, especially around all the cellular elements, are dilated, so that these lie almost free. This rarefaction of the connective tissue may well be the reason why the remainder of the cellular infiltration can now no longer be recognised, on pressure with the finger. In one of these papules I found a little true, golden cutaneous and brown epidermic pigment, but so little that it could not be regarded as new formed, or in any way connected with the healing of the syphilide. Where it is present, it helps to somewhat darken the spot.

We see then, that the histological termination of the papule does not correspond with the clinical. Not only does part of the characteristic plasmomatic infiltration remain, but, if my explanation of the taking up of basophilic granules in the homogenised cells and giant cells be correct, the constituents of the healing syphilide, which is undergoing regressive metamorphosis, actually show—probably only transiently—progressive tendencies. At any rate, the plasma cell of the syphilide is not that frail, short-lived thing which it is usually

considered. Rather, the nature of its regression, its conversion, by loss of the chromophilic substance, into a simple round connective tissue cell, with ordinary frothy protoplasmic structure, suggests that the syphilitic process only temporarily transforms many pre-existing connective tissue cells, by the taking up of certain substances, into plasma cells. During the active stage they distinctly multiply by division,* later they are diminished in number, and poorer in pathological contents, some persist, some are re-transformed into ordinary connective tissue cells, and the remainder are absorbed. The former provide the best basis of a histological explanation of the immunity.

II.—*The mixed papular Syphilides.*

(a). *The papulo-crusted Syphilide.*

The papulo-crusted syphilide is a modification of the small, or more often of the large papular syphilide, which often affects all papules, but sometimes only certain regions. In the latter case, it mainly affects those areas, which are also the seats of predilection of seborrhœic eczema ; the hairy scalp with the margin of the forehead, the centre of the face, the neck and shoulder girdle, the flexures of the joints, and so on. Occasionally I have been able to recognise uncomplicated seborrhœic eczema, along with such syphilides ; in others it was evident from the history.

Most of the papules are covered with thick, yellowish, soft, loose crusts, after whose removal they present an unusually light, often yellowish brown appearance and a softer consistence than the simple papules. After removal of the crust, they usually project more over the level of the surroundings, are richer in blood, and darker.

Histological investigation shows that these papules show very definite variations from the ordinary type, which may be due to a new additional cause. It may be that this is to be sought in the special condition of the skin of the individual, or, as I think more probable, in a mixed infection with epidermic parasites.

All the papules show, at the periphery, an unusually vigorous epithelial growth, which is shown by an enlarged ridge net and numerous mitoses. This acanthosis also affects those follicles and ducts which are accidentally located at the periphery of the papule, but only their upper ends, in connection with the epidermis. Towards the centre of the developed papule, the acanthosis gives way to its opposite, epithelial atrophy, for the papillæ and the whole papillary body swell up considerably and thin the epithelial ridges. Still, however, we find very irregular processes of epithelium, extending from the diminished ridges in different directions, sometimes downwards, which show

* It is very difficult to determine, whether the plasma cells divide by mitosis as well as by segmentation, for the few mitoses in the plasmoma show, as usual, the protoplasmic substance unstained, and thus the best criterium of the plasma cell is lost.

that, at the commencement, distinct epithelial proliferation had taken place in the centre of the papule also. The same significance have certain coarse irregularities of the surface of the older papules, when freed from the crust, knob-like elevations and dimpled depressions, the latter corresponding to broad, afterwards cornified epithelial depressions, the former to the œdematous papillæ between. To this primary hypertrophy and secondary atrophy, there are further invariably added, in the centre, other changes of the epithelium; general dilatation of the lymph spaces, slight swelling of the epithelium itself, especially above the papillæ, and a partly simple œdematous swelling, partly fibrinoid degeneration of the transitional and lower horny layers. The transitional epithelium and the basal horny cells swell out into formless plates, which, on section, have a diameter almost equal to the height of the large basal prickle cells, and are filled by a homogeneous clear substance, which still shows nuclear remains, or by a more thready fibrinous mass, when they usually also contain a few leucocytes.

Where this œdema, or fibrinoid degeneration of the cornified cells, is present, there is, of course, no keratohyalin or elëidin. Nevertheless the cells are surrounded by a cornified mantle—one of the many proofs that cornification may take place without separation of keratohyalin.

These changes in the upper epithelial layers neither extend equally over the whole surface of the papule, nor are they persistent. Layers of very different epithelial formation compose the crust, above or alongside of each other; normal, œdematous, and fibrinoid horny substance, and these are further permeated by spaces, filled with fragments of leucocytic nuclei. The crusts thus look like those of crusted seborrhœic eczema, and are difficult to distinguish from them.

The epithelial œdema is only an extension of the œdema of the papillæ, and it leads to appearances, at the height of the papule formation, not seen in the ordinary syphilitic papule. Instead of the papillary body being packed with plasma cells, we find a very œdematous connective tissue, with many typical spider cells, but only a few plasma cells. Usually these are found in direct contact with the blood capillaries, and, from the enlargement of their endo- and perithelia, with the taking up of deeply-stained substances, these present, in many places, in the centre of the œdematous tissue, the appearance of solid cellular cords, penetrated by a fine lumen. The lymph vessels and spaces of the papillary body are much dilated, the blood capillaries, only where collections and stasis of white blood corpuscles has taken place. In such places, especially at the apices of the papillæ, the capillaries are irregularly dilated, and the endothelial cells, adjacent to the white thrombus, are separated from the walls, lose their stainable substance,

acquire vacuoles and are finally completely dissolved. A regular marginal arrangement of the white blood corpuscles is here as rare as in general, and consequently the emigration is limited to certain points, and as a whole is slight, although distinctly more evident than in the other syphilides. There is great serous and sero-fibrinous exudation, with relatively few leucocytes.

The most important circumstance, almost characteristic of this form, is the limitation of all these processes, epithelial growth, papillary œdema, epithelial atrophy, disappearance of the plasmoma, œdema and fibrinoid degeneration, to the superficial part of the papule. Below the sub-papillary vascular net, there is little change. We find here the dense, perivascular and areate plasmoma, the formation of multi-nuclear and pale plasma cells, and occasionally of very large giant cells, the new formation of spindle cells and firm connective substance between, the passiveness of the deep epithelium ; all exactly as in the ordinary large papular syphilide. The margin between the œdematous, upper, and the dry, lower part of the papule is often sharp and is found at the level of the sub-papillary net. But in most papules the transition is more gradual, through a broad zone, in which the collagenous tissue is somewhat swollen, the lymph vessels moderately dilated, the plasma cells more abundant, but still scattered ; in this zone, perivascular, but no inter-vascular plasmomatic foci are as yet present. A small zone of pure, uncomplicated syphilitic plasmoma finishes off the papule beneath and laterally. But, however much the superficial parts of the papule are altered by œdema and disappearance of cells, we always find occasionally, large, pale giant cells, as a sign, that a plasmomatic area has previously existed here. Beyond doubt the crusted papules are among those which appear most frequently as obstinate recurrences.

The greatest interest of these crusted modifications hangs around the answer to the question, whether œdema of the cutis and epithelial changes first develope on the complete syphilitic papule and modify it, or whether they develope simultaneously with the more characteristic syphilitic changes of the deeper layers, or, finally, whether they precede the formation of the syphilitic plasmoma, so that the latter developes on an already modified base.

From the simple consideration of the papule at the acme of the process, one would tend, I think, to the first assumption, since we always find remains of the plasmoma, with giant cells, inside the modified upper parts. But the examination of the most recent papules has of course the last say in the matter, and this gives another answer.

Here, as was to be expected, the epithelial hypertrophy predominates, even in the centre. Numbers of mitoses are present in

every enlarged ridge. In addition, œdema is present, at least in the broadened papillary apices, in conjunction with a dilatation of the lymph spaces of the epithelium. In some places there are considerable numbers of leucocytes in the epithelium. The granular layer is well preserved, indeed widened in places, while the horny layer, considerably thickened, shows a scale, but not yet a sero-fibrinous crust. That these changes on the surface are the forerunners of the later crust-formation, and show that this is *not* secondary, is seen by the fact that the cutis shows considerable inflammation, but no symptoms common to the commencing syphilitic papule; in particular no well-stained plasma cells. The blood vessels in relation to the papule are much dilated; more so than usual in the fresh uncomplicated papule. They are lined with swollen endothelium, but are not surrounded by plasma cells. The papillary body and the cutis, so far as the papule reaches, are very cellular between the vessels, but the cells are rounded and spindle-formed connective tissue cells, with deeply staining contents, and without any areate or perivascular arrangement. At the same time the fibrillary tissue is swollen in the papules, often almost colloid, and is penetrated in a moderate degree by leucocytes, while mast cells are only found sparingly. Enough, we find in the main a chronic productive inflammation, but no inflammatory new growth, of the type of the infectious granulomata.

Only very occasionally is this uniform arrangement seriously disturbed. Here and there we find, without any connection with fresh plasmoma areas, large, quite pale giant cells, and, if the cellular infiltration is very carefully examined, we find, in among the plasma cells, pale multi-nuclear, breaking down, old plasma cells, which are no fresh development, and are to be recognised as plasma cells only from their likeness to the paled, dissolved and breaking down ones, which are familiar in the syphilides. Thus we have a very distinct remnant of a syphilitic new growth, in the middle of a fresh, uncharacteristic inflammatory infiltration, and evidently breaking down under its influence. This anachronism is, in syphilis, not remarkable. We learn that such papules form on the basis of the remains of earlier ones, and the remarkable thing rather is that the recrudescence of the local effect is not at first evident in the ordinary way by an increase of the plasmoma, but in its partial breaking down, secondary to a simple productive inflammation of non-specific character. Now we see the explanation of the pale giant cells, found in the œdematous papillary body, at the acme of the process. These have nothing to do with the new syphilide, they are the remains of a much older one.

Some older, already crusted papules are readily related to the appearance of the mature eruption, described at first. At the base and

at the whole periphery of the inflammatory papule, there appear, all at once, fresh plasma cells, which sheath the vessels and form small areas between them. These areas multiply, and appear more numerously in the transitional zone, scattered on the surface of the papule, while the œdema here continues to increase, the acanthosis vanishes, the epithelium undergoes fibrinoid degeneration, and the horny layer is converted into a thick fibrinous crust.

At the height of the papule we can clearly distinguish three different elements, namely—(1) remains of the older syphilide, in the form of pale, isolated giant cells and breaking down plasma cells; (2) an inflammation of the surface of the skin not typically syphilitic; and (3) the new syphilide extending from the base of the papule more or less towards the surface. The question asked above is consequently not so easy to answer as at first appears, for both the inflammation ollows the new formation, and that again the inflammation. But that it can be answered says, I think, much for the eloquence of histological appearances.

(b). *The papulo-crusted pustular Syphilide* (*Ecthyma superficiale*).

The etiology of this form is as much in the dark as that of the previous one. The so-called Ecthyma syphiliticum of recent authors, in my view, always indicates a mixed infection, and, since it is usually developed from the papulo-crusted form at its seats of predilection, especially the legs, I would regard it as the infection of such a syphilide with the germs of ecthyma. I have been successful in cultivating from it, not the ordinary pyococci, but other bacteria, whose relation to suppuration is still being investigated. Possibly they are the infectious agents of ordinary contagious ecthyma (Vidal). The occurrence of this form in vigorous young individuals, on the breast, back and face, shows, that this rare variety of the syphilide has no connection with a debilitated condition. Unless then we assume a peculiar quality of the skin, which the not infrequent occurrence of the ecthymatous transformation of the papulo-crusted syphilide on the leg alone, contradicts, we are almost driven to assume a mixed infection.

The numerous "ecthyma" papules in my possession all come from the leg of a female, elsewhere affected with papulo-crusted syphilis. Except for their suppuration, therefore, they show the appearance there described, of firm large papules which, deep down, are normally formed and dry, on the surface, swollen and œdematous. This basis of the syphilitic ecthyma pustule being familiar, we only need to describe the additional characteristic suppuration. This is superficial throughout; the abscesses usually lie inside the horny layer. Only in the centre do they, here and there, communicate with sub-epithelial masses of pus infiltrating the upper papillary layer. Thus the point of development of the suppuration is so limited, and the whole nodule so little affected

by it, that the superficial veins and capillaries, which do not lie directly under this collection of pus in the papillary body, neither show marginal arrangement of the leucocytes, nor contribute to the emigration. From the suppuration of impetigo, this is mainly distinguished by the pre-existent epithelial changes; epithelial atrophy, inter-cellular œdema and œdematous and fibrinoid degeneration of the older prickle, granular, and basal horny cells. The few layers of prickle cells lying over the œdematous papillæ, which are about to suppurate, are infiltrated with leucocytes; there are formed, here and there, small interspinal abscesses, filled with leucocytes and loosened epithelium. Further, leucocytes wander into the fibrinoid degenerated transitional epithelium, and form small abscesses. The crust now shows—in contrast to the simple papulo-crusted form—alternating with fibrinoid degenerated horny layers, others, densely packed with fragments of leucocytic nuclei. Directly above the basal horny layer there is a large collection of closely packed pus cells which, with a few loosened horny cells, forms an abscess of the horny layer. Where such exists, it is, on account of the previous epithelial atrophy, only separated from the purulent papillary body by a weak epithelial covering, which, infiltrated with leucocytes and often penetrated, may finally completely give way, whereupon the abscess of the horny layer is deepened, the purulent papillæ surrounded and eventually destroyed. Usually, in this superficial form of ecthyma, the matter ends with the exposure of the papillary body; the ulcer, deprived of its crust, appears, from the hypertrophy and œdematous swelling of the marginal epithelium, to be deeper than it actually is. The irregularity of the base depends on the irregularity of the papillary body already described of the papulo-crusted syphilide, which owes its origin to the primary irregular in-growth of epithelium.

The horse-shoe shape, which the syphilitic ulcers in general assume in healing, and which first appears in the ecthymatous ulcer, demands a special explanation. For here, the assumption of causes of disease extending serpiginously in the epidermis, which might explain the serpiginous form of the *progressive* papule, does not, of course, hold. Even when one cuts off the ecthymatous ulcer smoothly and horizontally with a razor, he can often observe that this artificial loss of substance heals from one side, and therefore assumes more or less the horse-shoe shape. If one runs over well-stained central sections of a series of these papules with the naked eye or with a low power, it is very striking, how almost invariably the one side of the papule is more faintly stained, and passes gradually into the healthy neighbourhood, while the other, more deeply stained, is more sharply margined. This is always best seen in those sections which are directly in the plane of

a vessel, and follow its branches. This corresponds to the facts, that the syphilitic papule is formed around the vessel as a basis, and that the latter usually reaches the surface at an acute angle. The papules therefore form, to speak geometrically, cones, which are obliquely directed towards the surface. Where the apex of the cone lies under the surface, there is found, perpendicularly to the surface, much more pathological material than under a point of the ulcer, which lies at the other end. Consequently, in the healing of the eruption, at that point of its border under which the apex of the vascular cone lies, the healing will be more tardy, since here most pathological material has to be absorbed. If I remove the whole base of the ulcer with the marginal epithelium, things are not altered; I have only shortened the oblique cone, there is still found at its apex the greatest quantity of the syphilitic infiltration, reckoning from here perpendicularly to the surface. The horse-shoe healing of the non-serpiginous syphilitic ecthyma pustule is therefore of quite another nature than the equally frequent horse-shoe form, which is taken by the serpiginously extending syphilide.

(*c*). *The varicelliform Syphilide.*

As such, we describe a secondary, small or large papular syphilide, in which the eruptions are, some or all of them, covered with varicellous vesicles, after whose drying up and scaling, they run the course of an ordinary syphilide. It is very rare. I had the opportunity of examining a spot from the neck of a typical case.

Since the histological appearances of this case are very peculiar, and could not be verified on a second specimen, I give them only briefly and with reserve.

It is not, as it appears, an epidermic vesicle, but a total separation of the epidermis at the seat of the papule. The base of this lesion of continuity is very transparent, for the epidermis as a whole is thinned, the ridges are flattened out, and, instead of the cylindrical basal cells, we find, as a marginal zone, small cubical, rounded, faintly-stained epithelial cells, which have partly lost their prickles, stain faintly, as if washed out, or are completely degenerated. The atrophy of the epithelium on the one hand, and an œdematous swelling of the papillary body on the other, causes a loosening of the whole epithelium, which explains the vesicular elevation. It is a form of vesicle which is found exceptionally in, among others, lichen planus, and stands at the border of our definition of the vesicle; we may indeed, though not in the sense which Auspitz has used for pemphigus, call it "*acantholytic*" or

"*cachectic vesicle formation.*" But it is questionable whether this represents the normal condition in the varicelliform syphilide.

Otherwise the eruption does not importantly differ from the ordinary syphilitic papule, there are fewer plasma cells, and the tissue, as a whole, is more œdematous and less hyperplastic than usual.

(*d*). *The varioliform Syphilide.*

This form of the papular syphilide is still rarer than the preceding, and is usually limited to certain regions. The vesicles are flatter than in the varicelliform variety, but their base is firm and swollen like a cushion. They are transparent, have a mother-of-pearl shimmer, with a dark centre, and therefore resemble vaccine vesicles on the 6th or 7th day of development, or quite young pocks. I had the opportunity of examining a papule from the scrotum, in a characteristic case.

Histologically, the resemblance to small-pox is much less than clinically. There is a monolocular, sub-corneal vesicle covering the whole eruption, but it appears to have run together from a number of primary vesicles lying over the papillary apices, for, corresponding to the ridges of the epithelium, toothed processes reach from the under side of the cover into the vesicle. The contents consist in the upper part mainly of leucocytes, in the under, of serum and fibrin. The base is formed by a prickle layer dotted with a number of tiny inter-cellular spaces filled with leucocytes and serum. At the periphery, where the prickle layer is thickened by enlargement of the epithelium, the inter-epithelial cavities are rarer than towards the centre. But right in the middle, the base of the vesicle is very much thinned by a cushion-like swelling of the central papillæ, the prickle layers are here stretched horizontally, and, owing to the exudation from beneath, have partly undergone reticular degeneration. On the other hand, there are here no intercellular cavities, and there is no penetration of the base of the vesicle. Evidently the shining through of the hyperæmic cutis, at this thin part of the vesicle base, produces the dark centre, and the vesicles stretched over the thickened periphery of the vesicular base, the greyish white mother-of-pearl appearance and the shimmer.

In regard to the formation of the vesicles, therefore, the varioliform syphilide in no way resembles the degeneration vesicle of variola, but is more related to the pressure vesicle of the bullous syphilide of infants, except that it shows leuco-fibrinous rather than leuco-serous contents. Except for a few probably unimportant collections of micrococci, in an uncharacteristic position inside fissures of the horny layer, I was unable to find any micro-organisms.

Apart from the vesicular formation, the excised spot corresponds,

in almost all points, to the typical, small papular syphilide. Only, the papillary body is more cellular than usual, and contains an abnormally large number of white corpuscles.

From the histological appearances, there is then hardly any necessary reason for ascribing the vesicular formation to the presence of a mixed infection, unless we regard the presence of fibrin as one. There is, at the commencement, an unusually excessive emigration of leucocytes, rapidly giving place to a fibrinous exudation. Of the organisms with which we are familiar, the morococci of eczema successfully inoculated would induce something like it. This must be settled by future investigation.

4. *Tertiary Syphilides.*

(a). *Introduction.*

The tertiary syphilides form a sort of general group, embracing everything which can be regarded as the result of the syphilitic invasion. But nowhere is it easier to demonstrate, than in those cutaneous syphilides, that they are only the rejuvenated remains of old syphilitic products, of the secondary, or even primary period. I have myself provided the first unanswerable proof of the transformation of the remains of an initial sclerosis, "in situ," into miliary dry caseating gummata. Further investigations by Neumann and myself have shown that it is the rule in all syphilides, that histologically recognisable remains, especially remains of cells, persist around the vessels after every syphilitic eruption, and in these I would recognise the explanation of the long immunity against new infection as well as the points of development of all tertiary new growths. While the specific irritant has no action on these remains, they may be stirred up to new formative activity by many other internal and external irritants.

Clinical observation has long taught us that this recrudescence of old remnants may take place in two different directions, which may be completely and sharply distinguished, histologically, although they are, even yet, incorrectly mixed up under the name of gummatous new formation.

The first and most frequent form, which I will call the *regular type*, exactly repeats, on a somewhat larger scale, and with slight structural variations, which are explained by the greater age of the affection, the type of the secondary papule, that is, it is associated with that infiltration along the vessels, which forms the framework of these, as of all secondary syphilides. And there is also, clinically, a gradual transition of the papular into this *tuberous* syphilide, both transitions through slight, unnoticeable variations of the single spots, as

well as a temporary transition, with the development of the individual late secondary papules, in situ, into an early tertiary tuberous eruption. The frame remains the same, the proceedings are similar, if not identical, the product is usually somewhat larger, but always firmer and more resistant and less open to spontaneous absorption, the result is a definite defect, an atrophy, while in the secondary syphilides absorption leaves behind it no atrophic tissue. There is nothing of a gummatous substance present, so that the name "gumma," used clinically, is quite a misnomer, having no histological basis. The tuberous syphilide resembles the papular in a firmer form; it is its pure, complete, late recurrence.

But there is a much rarer form of the tertiary syphilide, which, from an historically easily explicable, but incorrect view, has unfortunately been regarded as the typical tertiary form, even of the skin, while, at most, it only represents the main type for the hypoderm, that is, the *gummatous syphilide.* In this, the syphilitic new formation leaves the old routes of the circulation, limiting itself to isolated points, and extending concentrically from them, in the direction of least resistance. Evidently the gumma does not develope, like the tuber, from equally distributed remains of the secondary syphilide, but from a single point particularly or alone disposed to it; irregularly. Therefore, and in order to make clear my view, as opposed to the old conclusion, I would call it the *irregular tertiary type of the cutaneous syphilide.* This deviation from the otherwise "normal" formation of the syphilide alone suffices to explain all the other peculiarities of the gumma. Here, also, the cellular infiltration consists of plasma cells, but since these are not regularly distributed around all the vessels of the cutis, but are collected at individual points, the collagenous tissue there completely disappears. There is, in the gumma, a perfect division between plasmoma and fibroma, while in all the other syphilides both changes occur together, and are closely intermingled. We have developed a firm fibrous capsule, with soft cellular contents, and, in consequence of the greater pressure which the latter suffer from the former, a formation of generations of smaller and smaller cells, and finally, with regressive changes in the centre, drying or liquefaction. All these appearances, which also characterise the gummatous degeneration of internal organs, are, on the skin, simply the result of special different conditions. For the skin is a fibrous organ, and does not readily provide in its spaces the room required for the first development of the irregular, purely cellular nodules. But, if such develope, a limit is soon set to their increase in volume, they are early encapsuled and undergo dry caseation. But these cases are rare.

More common is an irregular plasmoma formation in the loose

tissue which sheaths the coil glands and loses itself in the fatty tissue. The gummatous formation then almost always developes from plasmoma remains, which accompany the blood vessels of the coil glands (new irritants from the coil glands ?), and extends itself from here, at first into the fatty tissue, later, following certain blood vessels, in finer cords towards the surface. Here the encapsulation by fibrous tissue is less, the plasmoma formation gradually assumes greater dimensions, a richer blood supply is present, and the result of all these conditions is finally the moist degeneration in the centre, the softening, liquefaction, the outward rupture, and the gummatous ulcer.

The gumma is related histologically to the tuberous syphilide, as the late syphilide is, clinically, to the early syphilide. It is more limited, and therefore all the more destructive. Where a gumma developes, the circulation is no longer fitted as a whole for plasmoma formation; instead of the diffuse reaction of the cutaneous area, we have a punctiform one, which has all the more deleterious action on the skin. The gumma is certainly a true tertiary formation, it is indeed the very end of the long chain of the syphilides; but it must not be regarded as the regular type of all tertiary syphilides. A gumma is certainly the surest proof that a syphilis is tertiary, for there is no further development of the syphilide; but its absence is no proof that any given syphilis must be secondary. Further, the simultaneous presence of both forms, the gummatous and the tuberous, close beside each other, is comprehensible, for local conditions play a great rôle in the development of both; I have often found the purely intra-cutaneous dry gumma accompanied by the tuberous form.

From this description of the development, we understand all these peculiarities which have always been rightly attributed to the gumma as opposed to other tertiary products; its preference for the hypoderm, its late and isolated appearance, its more rapid development and tendency to softening, the smallness of the cells composing it, and its relatively easy cure.

If we analyse the two main forms, we have to distinguish, first, the *simple* from the *mixed* syphilides. Syphilis tuberosa simplex shows these solitary or irregularly distributed, but rarely very numerous nodules, of coppery or raw ham colour and firm consistence, the size of lentils or more, which usually extend distinctly over the surface. After absorption, there remains for a long time a paler nodule, then a dark spot, finally an atrophic area of skin. If many nodules are closely arranged, they sometimes run together into a diffuse tuberous surface which may assume an elephantiasic appearance.

More important among the tuberous forms are the mixed, which, considering their superficial position, their long existence and their dependence on external irritation, is not remarkable. I regard as such, the circinate, crusted and vegetating forms, which in many cases certainly represent complications with seborrhœic eczema; and the ulcerated, as well as those both circinate and ulcerated. All these come under the so-called "Lupus syphiliticus."

Among the gummata we have, as already remarked, to distinguish a *drying* and *softening* form. The former always remains microscopical, the foci at most reaching miliary size. The softening gummata of the skin are the ordinary ones, which develope from the under margin of the cutis into the hypoderm; there are sometimes seen in the skin above them, if they do not burst outwards, small, encapsuled, miliary dry caseating gummata. Among the gummata there are also mixed forms, which possess neither special clinical nor pathological interest, since they are first seen after the bursting of the gummata, namely, the suppurating or phagedenic gummata.

(b). *The simple tuberous Syphilide.*

The best object to examine is an isolated, non-scaly, brownish red, raw ham coloured, smooth nodule somewhat elevated over the surface, and not too old, in order to exclude both the symptoms of the addition of other dermatoses and those of absorption.

We find, then, in the central sections, an appearance which closely recalls that of the syphilitic papule, for both the individual elements and their whole arrangements are the same. Here also, at the first glance, the diffuse plasmoma of the papillary body in the upper half of the skin looks like a new formation, developed first around the vessels, but later running together. It is here, as in the small papular syphilide, well circumscribed, seated between the epithelium and the under half of the cutis, in the form of a plump lentil, and sharply margined from the healthy surroundings. We find, here also, a central, tap-like vascular process, and a few considerable remnants, given off laterally to the coil glands. And with a high power we find the same elements: large and small plasma cells, paled plasma cells, and giant cells, spindle cells and thickened fibrillary tissue, along with very few mast cells and leucocytes. And yet we very soon see differences, which, although they are only quantitative, when carefully examined, thoroughly separate the two forms of the syphilitic new formation.

It first strikes us that the vessels, down to the capillaries, are wider than in the papule. This can hardly depend on the fact, that the external pressure, from the development of plasma cells, is less, for

in this connection the tuber differs very little from the papule. It must depend on a greater resistance of the vessel walls to this same pressure. As a fact, even the smaller vessels are thicker walled than normal; they are evident in the middle of the plasmoma, surrounded by a broad pale border, exactly as in the papule. Then the connective tissue rafters, which separate the individual plasma cells, are thicker and stiffer. In parts of the nodule a reticular appearance is the result of this arrangement of the firm connecting substance, similar to, although not so fully developed, as in the initial sclerosis. As usual an increased number of spindle cells accompanies this increase in the collagenous tissue. Certainly the capillaries in the preparation have collapsed and are densely surrounded by the plasma cells, but the gaping condition of the larger vessels is evidence that, in life, the capillaries were subjected to increased pressure, and were abnormally filled. This explains the deeper red and the greater firmness of the tuberous syphilide, in comparison with the papule.

Especially altered is the connective tissue of the papillary body, whose finer normal structure completely disappears. The collagenous fibres become as thick as those of the cutis, the blood and lymph vessels gape, as do the lymph spaces, so that the papillæ acquire an unusually firm, succulent appearance. In quite young papules, large plasma cells form a mantle for the blood capillaries; older nodules show the broader and flatter papillæ more filled with large, deeply-stained plasma cells. But in general they only appear in considerable quantities, late, after the surroundings of the sub-papillary net are completely filled with them, and they disappear in the same order, first at the apices of the papillæ. The elastic tissue disappears, as it does in the cutis, in the neighbourhood of the nodules.

The differences of the two new formations in the plasmoma and its derivatives are much less than in the fibrous part. It is certainly to be noted that the nodule exists much longer than the papule, and on comparing a nodule four weeks old with a papule of the same age, one would get the idea that the former contained far fewer degenerated plasma cells and giant cells. But the nodule goes through exactly analogous changes to the papule, only more slowly. The large, deeply-stained plasma cells become more limited to individual streaks and groups, and in their place appear numerous, small, less well-stained ones and giant cells, and in some nodules, when involution commences, one may meet with as many, forming, small and large, scattered or grouped giant cells, as in the papule. Even in the distribution of the large and small plasma cells and in the moderate number of the latter, the nodule does not differ from the papule or from other syphilides, if it has reached its acme. For here—in contrast to tuberculous lupus,

with its layers of large, small and paled plasma cells, and the predominance of the smaller ones—the large plasma cells are arranged in small collections and singly, scattered equally over the whole cell mass, and the pale cells partly develope from the large plasma cells without the mediation of small ones, which are not much more numerous than the large.

Mast cells and leucocytes are only found very sparingly in the nodule; the elastic tissue immediately perishes, the muscles and nerves remain intact. The epithelium remains passive; the super-papillary prickle layer is thinned and stretched. Between the papillæ, which are mostly swollen by the cellular and collagenous new formation, the inter-papillary ridges are first excessively thinned, and later completely atrophied. The coil glands always show a dilated lumen, and the epithelium is often loosened from their walls.

The tuberous uncomplicated syphilide, at the height of its development, is thus a dense nodule, composed of plasma cells and their derivatives, new formed fibrillary tissue with spindle cells, wide blood and lymph vessels and gaping lymph spaces. Its retrogression is still more characteristic, and not to be compared with that of any of the other syphilides. As already noted, the absorption of the plasma cells commences at the apex of the papillæ, which is gradually completely freed from them. But the papillæ do not then sink down, the firm scaffolding formed by the new formation of collagenous tissue retains them in their previous form and position, but it is now permeated by wide gaping lymph spaces. After the papillæ, the upper part of the cutis, which was early occupied by the plasmoma, is gradually freed, leaving behind it a firm collagenous scaffolding, mostly without cellular contents; here also there remains a porous connective tissue with wide lymph spaces. Only around the blood vessels, especially where they divide, around some of the papillary capillaries and regularly around the blood vessels of the coil glands, small collections of plasma cells resist the general absorption. The blood vessels in this œdematous tissue are of course much dilated.

The peculiar nature of this regression explains many clinical peculiarities, such as the swelling of the nodule at the commencement of treatment, while a firm, not much diminished remnant, often long resists treatment, then the spontaneous elephantiasic and sclerotic character of the skin, which appears after the long persistence of closely set tubers, and finally, the superficial atrophy, which invariably follows long standing tuberous syphilides. Then when finally, spontaneously or by treatment, the absorption of the collagenous scaffolding begins, the prolonged great dilatation of the lymph spaces and the tension and atrophy of the epidermis is shown by the sinking in of

the surface under the level of the healthy skin, just as in a scar. And the complete absence of pigment in these spaces is exactly as in the true ulceration scars, to which they have, of course, only a superficial resemblance. A comparison with lupus is of great interest. We have in lupus a fibromatous new formation, just as in the tuberous syphilide; but it does not appear during the process, but only after healing. In the syphilide the formations of plasmoma and fibroma proceed together; in lupus they replace one another, so that the plasmoma diminishes in the same degree as the fibroma grows into its interstices. Therefore such a regression as just described in nodular syphilis is not the rule in lupus. There the conditions are almost reversed, for, after the disappearance of the plasmoma, there appears a lumpy, tuberous keloid fibroma—the so-called hypertrophic lupus scar.

(c). *The mixed tuberous Syphilides.*

(α). *The tubero-crusted Syphilide.*

Even in the simple tuberous syphilides one finds, now and again at the commencement, as a complication, active epithelial growth, caused by some form of external irritation. I have before me a tuberous syphilide of the vulva, which, in addition to the typical plasmoma, shows an epithelial growth of the surface, and some sebaceous glands, distantly resembling the condylomatous transformation of the papules in this region. Further extension in this direction is shown by those tubero-crusted syphilides developing on a seborrhœic base, which mostly advance very slowly, in a typical circinate manner, and leave behind them an atrophic, white, shining surface.

In these cases there is, from the commencement, an increased acanthosis, so long as the papillæ still contain few plasma cells. Further, the papillæ are richer in spindle cells, and show a moderate number of leucocytes at their epithelial borders. The hypertrophied epithelial ridges are moderately, the supra-papillary prickle layer over the apices of the papillæ closely, beset with leucocytes, and the lymph spaces of the epithelium are widened. Where a greater formation of plasma cells and firm connective tissue has already taken place in the papillæ, the epithelial ridges are again atrophied, being converted, in sections, from thick processes into lanky columns; the supra-papillary prickle layer is also thinned. This is not so much due to the pressure of the swollen papillæ, as to the hyperkeratosis which, as in all parakeratoses, follows the acanthosis. The deeply penetrating horny layer encloses small streaks of leucocytes, and thus forms a crust, which is very like that of a psoriasis papule. The papillæ, which are particularly firm in all tuberous syphilides, but nevertheless usually present a broad flat form, are converted under the simultaneous pressure of the

syphilitic infiltration and the external hyperkeratosis, into very long, sometimes small, sometimes conically or globularly swollen structures. The frequent displacement of the epidermis and the papillæ in these proceedings causes a lesser adherence between them, which leads, here and there, to the formation of lacunæ between the epidermis and papillary body, such as we saw in the crusted papule.

In addition to the acanthosis, the limitation of the cellular infiltration to the papillary body and a small zone of the cutis underneath, distinguishes the mixed crusted tubers; this plasmoma does not reach further down than in the recent small papules of the secondary period. The under part of the cutis always remains free from plasmoma, so that—and this is the third noteworthy point—the plasma cell infiltration surrounding the coil glands appears to be quite isolated.

All these peculiarities point to the fact that some external irritation has penetrated under the epithelial covering, which causes first the acanthosis and parakeratosis, then the slight leucocytosis of the surface, the greater number of spindle cells in the papillæ, and finally locates the plasmoma close to the epithelial surface (inclusive of the coils. The crusted tuberous syphilide is—excluding the infiltration around the coils—a more superficial formation than the uncomplicated nodule, and, were not plasma cells and giant cells present, would be easily confused with seborrhœic eczema. This variety of the tuberous is less distinguished from the crusto-papular syphilide than the simple tuberous is from the simple papular. The additional secondary symptoms tend very much to obliterate the finer differences of the specific, syphilitic new formation in both cases. In this connection I must again lay most weight, not on the plasmoma, but on the spindle cells and fibrous new formation, which, in the tubero-crusted forms, especially in the papillary body, is larger in quantity, and in quality, denser, firmer, and drier; consequently in the latter the lymph vessels and spaces are less wide and gaping.

(β). *The fungating tuberous Syphilide.*

The fungating tuberous syphilide is a further extension in the same direction. I had the opportunity of examining a typical example, of twenty years' duration, which occupied the whole scalp. This affection, which, on account of its slight reaction to specific treatment, had been regarded as non-syphilitic, showed, in this case, its true nature, partly by a few crusted tuberous syphilides of the trunk, partly by histological investigation.

On the marginal parts of the fungating syphilide, adjoining the healthy skin, where the papillomatous character of the new formation passed into a simple crusted one, the histological appearances corre-

sponded exactly to those just described: a superficial cellular infiltration, consisting almost exclusively of large plasma cells, along with isolated infiltration around the coil glands, moderate epithelial growth and moderate leucocytosis from the vessels of the fibrous papillæ, and thickening of the horny layer, with numerous leucocytic enclosures. Further in, in the papillomatous regions, on the contrary, the changes in the cutis and epidermis reached the acme of their development. The plasmoma here was much denser, so that in the upper part of the cutis it almost completely concealed the collagenous substance, it extended further through the whole cutis in dense processes down to the region of the coil glands, completely surrounding them, and it clothed the hair follicles of the scalp, which mostly retained their hairs. The infiltration consisted almost exclusively of large, deeply stained, cubical, closely packed plasma cells. Only the upper ends of the usually enlarged and elongated papillæ were relatively free from the plasmomatic new formation; they contained only few leucocytes, but more collagenous substance and spindle cells. Their elongation and enlargement was produced by a vigorous acanthosis; the proliferated epithelial ridges were cornified far down, so that the very thick horny layer was wavy, like the surface of the cutis. The secondary falling out of the horny wedges from their inter-papillary beds completed the papillomatous appearance of the surface, which gives to the syphilide its peculiar type and name. The permeation of the horny layer with leucocytes was not particularly marked in this case.

In the fungating, tuberous syphilide, the progressive changes possible in syphilis are developed to their fullest extent; regular dense collections of large, deeply stained plasma cells enclosed in sparse, firm collagenous connective tissue, and margined by excessively cornified, proliferated surface epithelium, without any indication of *giant cell formation*, caseation, absorption, or breaking down—probably a better demonstration of the possible durability of syphilitic new growths (in contrast to the fact of their general frailty) could hardly be supplied. But the fact that, in the case before us, this new formation had lasted for twenty years, in spite of frequent attempts at cure, surely indicates definitely, that some special, excessively chronic irritation—such as the existent seborrhœic catarrh—must have favoured the growth, keeping it constantly young. And further, we must conclude, in view of this extreme resistance, that the frailty and the spontaneous disappearance of other syphilides is not to be measured by the character of the plasma cells (cases of lupus and other granulomata may go on unchanged for years and decades).

Under certain circumstances, the epithelial growth which attacks

tuberous syphilides may, without atrophy of the epithelium, undergo a peculiar change, which causes it to resemble certain cancers, viz., rodent ulcer. The plasma cell growth in the papillæ, in these cases, extends further, thinning and elongating the epithelial ridges, until they present thin, pointed, anastomosing processes, deeply penetrating the plasmoma. Only with appropriate special staining does one note, in the maze of plasma cells, spindle cells and broken down epithelium, that a thin layer of the latter, cornified, always clothes the new formation. This appearance somewhat recalls the effect of the advancing plasmoma on the epithelium in some initial scleroses, in which the primary acanthosis is strikingly developed.

(γ). *The tubero-crusted ulcerating Syphilide* (Ecthyma profundum).

The ulcerated form of the tertiary syphilide, like that of the papular, almost invariably developes from the crusted modifications. Only, before ulceration, there is here no proper pustulation, as is usual in the papulo-crusted syphilide, but, when the apparent crust is removed, we find already, on the skin, an excavated ulceration; the skin rather collapses than bursts outwards. This circumstance depends mainly on the fact that here the ulceration is not induced by secondary infection from without, but that a disintegration, similar to that in gumma, directly succeeds the crusted transformation of the tuberous syphilide. This form also is only present localised, usually extending in serpiginous lines, on the scalp, but it may also occur elsewhere, in isolated plaques, the size of a sixpence to a shilling.

Microscopical examination shows, at the border towards the healthy tissue, the ordinary appearances of the tubero-crusted syphilide or even only of the simple tuberous, a perivascular plasmoma in a firm, cellular connective tissue, enclosing groups of paled plasma cells and a few large giant cells, a moderate epithelial proliferation, always indenting the somewhat swollen and not very cellular papillary body, some œdema of the prickle layer and slight thickening of the horny layer. Nearer the ulceration we find the plasmomatic cellular collection denser, even filling the whole thickness of the cutis, and the prickle layer still more thickened. But at the same time there appears a *marked œdema* of the cutis and the epithelium, and this is most developed towards the surface, though by no means limited to it, as in the simple crusted syphilide. The œdema is further almost purely interstitial; it loosens the connection of all parts of the skin, without leading, as in the tubero-crusted, and still more in the papulo-crusted forms, to a parenchymatous swelling of the collagen, the spindle cells and epithelium. Thus, the nearer one gets to the ulceration, there are formed larger and larger spaces inside the prickle layer and the

papillæ, between the plasmoma areas and their surroundings, as well as between the individual plasmoma cells, which thus lose much of their staining substance, between the giant cells and their neighbourhood, and finally around all the hair follicles, sebaceous and sweat glands, which lie in these lymph spaces, almost free, and in many places as if nibbled and weather-beaten. The epithelial ridges also are washed at their apices by the tissue fluid, and broad lymph spaces extend irregularly from here towards the horny layer. This is also swollen up with serum over the œdematous region, and converted into a fibrinous crust, containing a moderate number of leucocytes, which, on account of the want of epithelial after-growth, remains thin, but from the presence of fibrin has a certain hardness and firmness. But

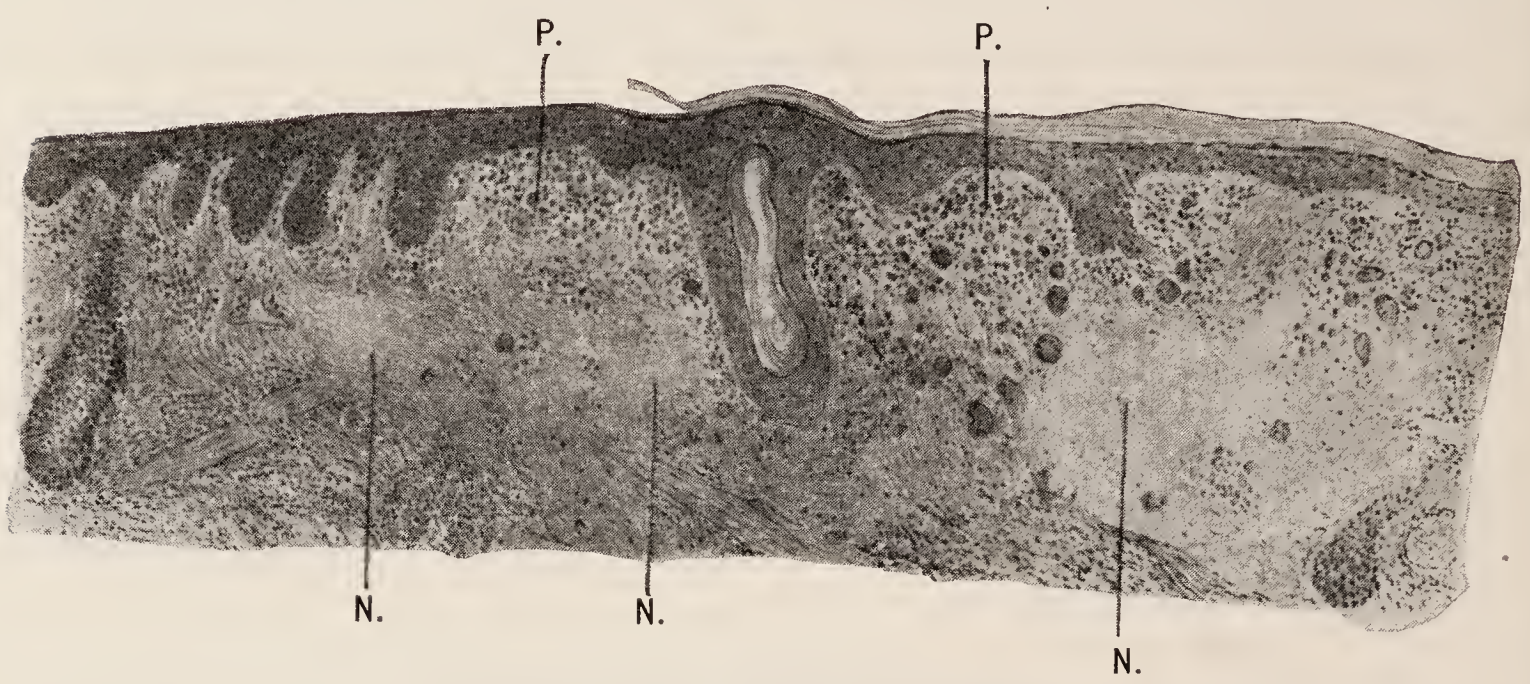

FIG. 23.—Tuberous tertiary syphilide.

N. Necrobiotic foci surrounded by giant cells. *P.* Plasma cells.

what gives to this œdematous, folded tissue a quite peculiar appearance, are large areas, irregularly distributed through the cutis, in which wholesale degeneration is taking place. These at first appear not unlike the small miliary cutaneous gummata, seen occasionally in the tuberous syphilides, indeed it is not improbable that here and there such are enclosed in the degenerated areas. But on the one hand, the irregular forms, the many processes and the wide extension of these areas, on the other, the circumstance that, in many of them, not only the remains of cells but of much inter-cellular substance is enclosed, show that we are not dealing simply with gummata of the skin, previously dry, which have become œdematous, but with *a widespread degeneration of a peculiar nature*, characteristic of this syphilide. Staining no longer clearly distinguishes cell substance and collagen in these areas; they are converted into badly staining, granular and thready masses, which can only be distinguished here and there,

because the interstitial œdema has loosened their connection. With a high power they look like dead, macerated masses. Most of the nuclei in them have perished, and the homogeneous nature and relative absence of nuclei gives them, even with the low power, a resemblance to the cutaneous gummata. But neither do they give the impression of coagulated masses, in spite of the disappearance of most of the nuclei, we have certainly not to do with a coagulated necrotic mass, which the saturation with fluid might suggest. Nor do they give the fibrin reaction. Their limitation is quite irregular, the areas extend in all directions, small projections and processes into the simply œdematous neighbourhood are mostly margined by pale but still well preserved plasma cells, and are almost invariably surrounded by a ring of large giant cells.

I must therefore regard these degenerated areas as "macerated plasmoma nodules" of the skin, with whose appearance the deep destruction of the whole cutis is introduced. This is the highest degree of homogenisation and softening. Lower grades are seen everywhere in the neighbourhood of the innumerable small and large spaces in the epithelium and connective tissue ; the staining substance has mostly disappeared from nucleus and cell substance, the cell contours are blurred, the collagenous substance is swollen and difficult to separate from the protoplasm, the whole tissue has an equally cloudy, weather-beaten appearance. This now goes on to complete degeneration, large, almost loose parts of the cutis and epidermis break off ; the addition of suppuration is by no means necessary to explain the final breaking down, although no doubt it may be present. But it does not appear to be the rule, for in the serpiginous forms a regular undisturbed scar formation immediately succeeds to the ulcerative breaking down of the plasmoma. In the isolated tubers of the genitals and the head, this degeneration appears to be earlier complicated by the admixture of other organisms, though neither more rarely nor more often than in the degeneration of the gummata.

Accordingly I regard the tubero-crusto-ulcerated syphilide, this certain manifestation of the tertiary period, only as the last untainted result of the tubero-crusted syphilide. That the crust-forming œdema leads here to the breaking down of the new formation, while otherwise it only leads to external, dry, lupus-like, and in the papular syphilide only to eczema-like forms, evidently depends on the age of the affection and the senility of the tissue, invaded by such an old syphilis. While the epithelium and the plasma cells of the connective tissue are always renewed and rejuvenated, and, in the tuber, appear just as they did in the papule and roseola, *the intercellular tissue continues to grow old*, although certainly a limited, persistent power of replacement may be

developed. It is *this old collagenous tissue*, which finally no longer resists the chronic œdema, whose destruction first loosens the parenchyma of the tissue, allows it to be more sodden, and thus invites decay.

(d). *Gumma.*

There has been great confusion in the definition of the gumma of the skin. Since the gummy masses, which were discharged from abscess-like tumours of the subcutaneous tissue, were considered as characteristic of tertiary syphilis as those gummosities of the bones which were familiar to the earlier syphilologists, there has always been a tendency to recognise, where possible, gummatous changes in all the tertiary products of cutaneous syphilis. The clinical expansion and extension of the definition of tertiary syphilis has therefore, since exact histological examination did not accompany it, almost necessarily attributed to many tertiary products a gummatous character, which they do not really possess.

I have already noted in the introduction, that the great majority of tertiary products, namely, all those which I have described under the name of tuberous syphilides, only exceptionally soften. The question arises in the general definition of gumma, whether, strictly preserving the name, we should only in future regard as gummata, softening masses of a tertiary nature, or not. In the skin it is simple enough, for here those degenerated products of tertiary syphilis, which have no gummatous type, are clearly enough distinguished, and appear to deserve a place of their own.

But if we compare the histological appearances of those tertiary processes of the skin, which lead to degeneration, with the corresponding appearances in other organs, which are more homogeneous than the skin, *e.g.*, the liver, it is evident, that the differences, which are so distinct on the skin, are there completely blurred by transitions. They depend then, not on difference in the degeneration processes, but on the different nature of the constituents of the skin. And further, even in the favourite seats of the gumma proper, in the subcutaneous tissue, tertiary products, exactly alike histologically, do not always show in the same degree, microscopically, the gummatous type, but a breaking down, dirty debris, just like that of the gummata of bones.

Although I hold it then absolutely necessary to limit and strictly define the far too wide definition of gumma, I would still regard a definition, which was only based on the macroscopically gummy appearance of the discharged products, as too narrow and unnatural. It must at least include not only the softening, but also all the dry, caseating tertiary products. The latter have been little noted, indeed their

presence in the skin denied. Their main seat is the middle of the cutis, here no other degeneration than the dry caseous appears to occur.

But even many tertiary nodules in, or at the border of the subcutaneous tissue, if the blood supply is insufficient, often enough undergo drying up, and not, as usual, softening. If any one wishes to convince himself of the close connection of these appearances, he should only compare, with a good protoplasm stain, the gummata of the skin, in the narrowest sense of the word, with the dry caseous areas, as found in the liver.

My definition of cutaneous gummata is consequently the following:—*Tertiary syphilides, which grow irregularly and concentrically from individual points, without dependence on the vessels of the skin, are peripherally enclosed by thickened collagenous tissue, and consist centrally of particularly small plasma cells, which gradually degenerate, and finally dry up into whitish yellow, firm areas, or soften into greyish yellow or yellowish red masses.*

The *drying gumma* of the skin, I have as yet only found in the cutis proper, in small sub-miliary areas. It appears to be able to develope in the tertiary period from all larger remains of cellular infiltrations, which are enclosed by thicker fibrous processes, and to commence its development without receiving any corresponding increased supply of blood. Its type is supplied in those small caseous areas, which I have noted above, in the results of the initial sclerosis. No doubt that case is unique, but it is none the less important, since it represents the results of an initial sclerosis left to itself for many years.

It may be quite easily seen, that only the smaller part of the caseating area has developed concentrically around the blood vessels. Most of it represents encapsuled and slowly degenerating remains of the plasmoma between the blood vessels, which are enclosed by thickened connective tissue, free however from cellular infiltration. The periphery of the area is still formed by plasma cells, mixed with giant cells, which, diminished and homogenised, pass abruptly into the dry central mass. In this latter, which has a spherical, oval, frequently centrally constricted form, the small nuclei are only faintly, and the cell bodies no longer demonstrable by basic colours, while the whole centre, in contrast to the borders, greedily takes up acid stains. Very fine sections show its composition from pressed together, dried up cells, still recognisable in the centre, without any collagenous substance. Taken together, these minimal caseous areas represent a nodule the size of a bean, of considerable hardness, though not so great as that of an initial sclerosis at the height of its development.

After the initial sclerosis, the fibromatous tuberous syphilide leads soonest to the development of the dry cutaneous gumma. I have, at least as yet, only found caseous areas in those which had developed in the middle of the infiltration of plasma and giant cells. Some of them are about the size of small coil glands, but most of them have run together into hour-glass-shaped, larger areas. Some cells, or rather some nuclei may be, with difficulty, stained by basic colours. The areas often enclose wandering cells and remnants of collagenous and elastic fibres. The latter are found, exactly as in lupus, as the centre of the giant cells, which surround the areas, and, in their nucleated summit, are most allied to the plasmoma of the periphery, in their a-nuclear, yellowish, dry cell body, to the caseous centre, into which they may pass. There is no doubt that these areas may remain behind in the healing of the tuberous syphilide, and then persist as miliary dry gummata.

While, therefore, typical gummata of the skin may exist alongside of tuberous syphilides, and directly develope from them, all cellular infiltrations of the cutis which develope in connection with large subcutaneous gummosities are by no means to be regarded as gummata of the cutis. It depends, so to speak, on their individual fate. If the areas are rounded off inside the encapsuling tissue, if the cells multiply, with diminution of their size, and completely degenerate in the centre, then we have a gumma. But if the cellular infiltrations are only converted into loose groups of homogenised plasma cells and giant cells, which slowly undergo absorption or even restitution, we have before us nothing more than the remains of a tuberous syphilide, in spite of the neighbourhood of true, subcutaneous gummata.

We may briefly sum up the *softening* gumma of the skin. Its point of origin is, in most cases, to be sought in the remains of the coil gland infiltration, its main seat is the hypoderm, which gives way before it. Where the skin lies near the surface of a bone, without any thick fatty cushion, as on the forehead, the tibia, the sternum, the clavicle or the olecranon, there the gumma of the subcutaneous tissue spreads to the periosteal vessels and directly extends into a distinctly prominent, hard growth of the periosteum, which may rupture externally just as readily as an originally cutaneous one. At the height of its development the gumma forms an abscess-like, fluctuating swelling, whose central point lies at the under margin of the cutis or in the hypoderm. The surroundings are relatively normal, but the vessels of the neighbourhood are surrounded by plasma cells, and the larger and deeper lying ones thickened in their walls. Nearer to the gumma, there are formed from the adventitial infiltrations small isolated areas, which chiefly surround the coil glands. Further, the connective tissue

bundles show a greater thickness, homogeneousness, stiffness and refraction, as well as a deeper stain with many colours, so that they must be considered as having partly undergone hyaline degeneration. They project in many places into the gumma, which also contains many sclerosed and hyaline degenerated connective tissue bundles, which are completely isolated from their surroundings and rounded at their ends, as if melted. At most parts of its circumference, the gumma commences abruptly with plasma cells, which are well-stained but distinctly smaller than the peripheral cells of syphilitic infiltrations usually are. From here the dense mass of plasma cells extends uninterruptedly to the centre of the area, with the slight addition of the remnants of connective tissue referred to, a few leucocytes and mast cells. Only here and there, at the periphery, is the uniformity of the area broken by larger vessels, along which the cellular infiltration regularly extends. Where it extends from the under part of the cutis into the fatty tissue, it is usually less dense, permeated by the remains of fat cells and partitioned by the thick connective tissue processes of the hypoderm. The coil glands are easily recognised in the dense cell masses, but finally they also are severely affected, their epithelium being loosened from the membrane, thrown off, badly stained, and finally converted into debris. The inner mass of cells in the gumma is by no means to be regarded as necrotic. They certainly do not stain so well as the peripheral cells, but their nuclei, even in the centre, are still well stained. We see that the main change concerns *the almost completely liquefied inter-cellular tissue.* Its disappearance explains the softness and fluctuating, abscess-like character of the growth, although there is no true suppuration. In fine sections, from which the celloidin has been removed, large parts of the central mass of cells always fall out, and there is thus a cavity, which did not exist in life. At these broken edges, one sees best how the constant production of plasma cells leads to complete disappearance of the collagenous tissue. The "gummatous" mass consists of a debris of cells suspended in a fluid inter-cellular substance, the tissue juice; the less fluid present, the drier and yellower, more "caseous" becomes the whole mass.

As the liquefaction of the collagenous tissue gradually extends outwards along certain vessels of the cutis, the cutis is gradually thinned, and the gumma bursts. Previous to this the vessels of the surface dilate, and, according as more or less external irritation is present, a considerable immigration of leucocytes takes place into the area. But true suppuration only sets in after the rupture, when pyococci are secondarily added, and thus we have only rarely, even in the sinuous ulcers, a considerable production of pus. Evidently the gumma, like

the syphilides in general, presents no specially favourable soil to the ordinary pyogenic organisms. The central softening of the gumma is explained by the free supply of nutrient fluid, the over-production of masses of cells, and their liquefying action on the inter-cellular substance. I could no more determine a true necrosis in the centre than that hypothetic endarteritis, which is assumed by many authors to explain it. I have indeed, like Tommasoli, never found endangiotic processes in the neighbourhood of the gumma. The cellular growth I must regard as the result of amitotic cell division, since immigration is, as we have seen, very sparing, and I have never found mitosis.

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Tuberculosis.

I.—Lupus; Tuberculosis Vulgaris Cutis; Typical Primary Tuberculosis of the Skin.

Although not so common as secondary tuberculosis of the skin (scrophuloderma), lupus is nevertheless the type of tuberculosis of the skin in general. It presents the commonest and most characteristic reaction of the skin to the *direct* inoculation of the tubercle bacillus (for example, by the stings of insects on the cheeks of children, by wounds received while examining tubercular bodies, by pieces of broken glass which have been infected by sputum, by piercing of the ears with infected needles, by scratching when other tubercular skin diseases are present, by the accumulation of secretions in the neighbourhood of tubercular fistulæ, &c., &c.). After a transitory inflammatory swelling, there slowly appears a soft, yellowish-brown, translucent spot of the size of a mustard seed to that of a lentil. It is more or less deeply embedded in the cutis, and is characterised by remarkable indolence and persistence.

Speaking broadly we can clinically distinguish two main forms, the **circumscribed** and the **diffuse**, between which there is, however, no very sharp margin, and they may even be combined in the same case, the disease being in one part sharply margined, while in another it tends to spread. The circumscribed form is clearly defined from the healthy surroundings, sometimes by a very sharp margin. The surrounding skin is normal or anæmic, so that the actual colour of the spot is clearly seen, as is also the difference in transparency and consistence. This pure, uncomplicated, typical form of lupus is met with particularly on the extremities, in very anæmic individuals, as a recurrence in scars or in the form of scattered satellites around larger lupus areas.

In the second main form of lupus, the typical spot with its peculiarities is not so prominent, for a persistent hyperæmia masks its colour, translucency and isolation. If the vascularity be removed by pressing on the part with a glass slide, the brown, translucent spot comes into view, no longer however so round and sharply circumscribed, but spreading out in a radiating manner into the healthy tissue, without any definite margin. In connection with the greater vascularity of the surroundings and the less sharp margin of the a-vascular spot, contrasted with the vascular neighbourhood, there are two further peculiarities of this (frequent) form of lupus—1st, its tendency to the formation of crusts, and 2nd, its extension at the periphery, and to these is due the more serious prognosis of this form and the absolute necessity of treatment.

In rare cases of this second form, the cellular lupus growth is comparatively insignificant compared to the accompanying widespread, persistent, superficial erythema, which does not readily go on to exudation (Lupus erythematoides, Leloir).

The histological examination and the appearance of the two main forms further teach us, that the additional symptoms just described in the second form may all be attributed to the one factor of the free penetration of blood vessels into the altered lupus tissue. We know, since Koch's discovery of tuberculin, that the chemical constituents of the tubercle bacillus, which is part of the lupus tissue itself, are quite sufficient, without the aid of other inflammatory irritants, to induce in the lupus tissue a marked sero-fibrinous inflammation, with the formation of crusts, in fact the appearance of crusted "eczematous," "impetiginous" lupus in the highest degree, and that the inflammation sets in the more readily the more vascular the lupus is. On the other hand it is plain, that the lupus, where it is not encapsuled by a firm membrane of compressed healthy tissue, will extend by the lymphatics more readily into the neighbourhood; but these are the cases, where the

blood vessels of the neighbourhood are not altogether obliterated, but run between the elementary, always a-vascular nodules.

On these grounds the grouping of all the, so prodigally named, forms of lupus into two categories, one *circumscribed* and *tending* to *encapsulation*, the other *diffuse* and *tending* to *extension*, is the one which strikes a *fundamental difference* in their clinical, prognostic, therapeutic and histological relations. They do not indicate two different varieties of tuberculosis of the skin, but the extreme development which the reaction of the skin shows to the inoculation of the tubercle bacillus, under and between which all the different forms of lupus may be grouped.

After the differentiating factor of the *vaseular supply*, we have to note the occurrence of two processes, which, although in no way aiding the diagnosis of lupus, lead, when present, to very characteristic forms; epithelial growth and *hypertrophy* of the *collagenous tissue.* The first alone is often combined with vascular lupus, *e.g.*, of the cheeks, without giving it any particular stamp; it then forms only a histological addition. But on the ends of the extremities, near the seats of predilection of the circumscribed encapsuled lupus, where, in consequence of the physiologically greater cornification, a *more marked hyperkeratosis* is almost invariably added to the epithelial growth, and the horny parts of the epithelial ridges fall out, there developes a new growth with a warty surface, in which the characteristic colour and softness of the lupus is clinically lost, as the epidermis is more developed. This form of lupus, to which many post-mortem warts belong, shows firm, pale or bluish red nodules, which are at first covered with a callous, thickened horny layer. After a long time they usually heal in the centre with a fine scar, while the growing border extends in papillomatous form. From the crypts between the warty, obliquely lying, horny cones a purulent fluid may sometimes be expressed, but there is never suppuration of the nodule, nor do furuncle or phlegmon ever succeed to this form of lupus, or to the true tubercular, post-mortem wart. It is not, as Riehl and Paltauf, to whom we owe the best description of lupus papillomatosus, suggest, a mixed infection with ordinary pyococci (staphylococci), although these may be cultivated from the secretion, but a mixed infection with the morococci of eczema, which may be always found in the horny layer and in the small sub-epithelial and epithelial abscesses, when this secondary superficial inflammation is added to lupus verrucosus. It is owing to them that this inflammation always remains superficial and never extends into the small hair follicles of the back of the hand and fore-arm, that the emigration of leucocytes is never excessive, that neither impetiginous nor furuncular abscesses are developed, but, only where the hyperæmia is greater, a

fibrinous inflammation of the papillary body, with epithelial growth and slight leucocytosis. The regular presence of "large cocci" in the horny layer, which often formed large balls (Riehl and Paltauf), shows that these authors had before them morococci, and not staphylococci. In wide-spread cases of lupus verrucosus, when the thick horny warts fall off, we may see the papillomatous form passing again into ordinary lupus nodularis, just as in healing. Then the normal colour and consistence of the lupus are at once clinically evident.

With the addition of fibromatosis, which succeeds, preferentially, to the diffuse hyperæmic form of lupus, especially after operative treatment, there develope keloid-like, bluish red or ivory white swellings, running across the remains of the lupus, and plates replacing the soft lupus tissue, which are clinically described as Lupus hypertrophicus, tumidus, scleroticus, or simply as lupus scars. But its reaction to tuberculin, as well as histological examination, shows that this connective tissue is very different from a true lupus scar.

To these more regular changes the *sero-fibrinous exudation* already referred to brings varieties. Owing to the œdema and the exudation coagulated in the epidermis, the lupus swells up just as much (cases of lupus tumidus, turgescens, elevatus), as from the increase of the cellular infiltration of the lupus tissue proper or from epithelial proliferation. After removing the fibrinous crust, there is seen a shining, reddish, eroded, moist, secreting, eczematous, epithelial surface, which, in the absence of traumatic, medicinal or operative interference, shows neither suppuration, necrosis, nor loss of substance. Lupus "exulcerans" or "exedens" does not therefore belong to the *typical* uncomplicated lupus, if we understand by ulceration a loss of substance from suppuration and necrosis of the connective tissue. These names should be limited to the cases accompanied by suppuration or necrosis of the whole lupus tissue, caused by chemical or operative influences or mixed infections (Lupus vorax, phagedænicus, Leloir), and the others should be described as Lupus crustosus, whether they have themselves taken on this form or it has been brought about by the superficial action of tuberculin.

In addition to the just described, a-typical, rare termination in *secondary ulceration*, we have to regard *simple absorption* and the leaving behind of an atrophic skin, a so-called scar, as the ordinary typical result. This result is the normal course, particularly in the circumscribed superficial forms, and while the lupus in the centre thus heals, it advances, very slowly, at the periphery, attacking the healthy skin without distinction (Lupus serpiginosus). These spontaneous scars of the superficial, benign forms of lupus have a peculiarly samite-white, cushion-like character. The hyperæmic diffuse form rarely heals

spontaneously, and artificially induced scarring is usually irregular and beset with scar keloid. Even the lupus fibroma, Lupus scleroticus, may be directly absorbed and converted into scar tissue. The spontaneously healing lupus is therefore the Lupus resolutivus, which is not so correctly named Lupus exfoliativus, in order (unnecessarily) to indicate a contrast to Lupus exulcerans. It is evident that no lupus can disappear by exfoliation; this is only one of the symptoms, and one of little importance.

We have therefore to describe, in order, first the two main forms—

1. Lupus circumscriptus, nodularis;
2. Lupus diffusus, radians; and, as an appendix of the latter form,
   Lupus erythematoides Leloir, Lupus under the mask of an erythema perstans.

Then further changes which are added to these mains forms, in greater or less development, partly due to the tubercular poison itself, partly to the secondary effects of processes stirred up—

(*a*). The epithelial hypertrophy of Lupus verrucosus.—Lupus carcimoma.
(*b*). The acute inflammation of Lupus.—Lupus crustosus.—Lupus after the injection of tuberculin.
(*c*). The fibrillary sclerosis of Lupus.—Lupus scleroticus, elephantiasticus.
(*d*). The secondary suppuration and liquefaction of Lupus.—Lupus exulcerans, Lupus vorax, Lupus phagedænicus.
(*e*). The absorption of Lupus.—Lupus resolutivus.—The lupus scar.

(1). *Lupus circumscriptus, nodularis.*

To the clinical form of lupus circumscriptus there corresponds, histologically, a form of tuberculosis, composed of sharply margined, isolated, elementary nodules—Lupus nodularis. It deserves the first place, for in each of these elementary nodules all the structural elements characteristic of lupus are found together in their purest form. Among the connective tissue, without any necessary relation to a blood vessel, there is first formed a rounded, compact collection of large, almost cubical, plasma cells. The smallest of these areas, which are found in the neighbourhood of larger masses of lupus, or as recurrences in the scars, consist of 40-100 or more closely packed cells, with unusually large and very granular cell bodies, and one, rarely

two, large vesicular nuclei. At the seat of these elementary nodules, the elastic tissue is completely absorbed, and the collagenous all but completely, so that the cellular parts lie together, almost naked, in a fine-fibred scaffolding. Although the normal constituents of the skin are here completely absent, they are perfectly well preserved immediately outside the nodule; the margin between healthy and diseased skin is as sharp as possible. Neither blood nor lymph vessels can ever be followed into these elementary nodules, although they often lie alongside the vessels, and develope from their adventitial cells. But the vessels, like the collagenous tissue, so far as it is not absorbed, are pushed to a side.

Thus are explained the clinical peculiarities of the lupus nodule. The absence of white fibrillary tissue makes the skin transparent at the seat of the nodule; the dryness of the purely cellular nodule is shown in the yellowish brown colour, and the absence of marked hyperæmia around and above the avascular nodules allows the brownish colour and the translucence to be recognised, without, as in the syphilitic plasmoma, the addition of a reddish tinge.

As these elementary plasmoma nodules increase, there invariably appear degenerative changes in the centre, partly from direct transformation of the plasma cells, partly after these have previously gone through a process of proliferation. The terminal product—the *degenerated plasmomatic area*—is the same, allowing for the proliferation of the plasma cells. The plasma cells divide, here as elsewhere, first with, later mainly without mitosis. Even with perfect staining of the mitoses of the epithelium and the surrounding cutis, I have only rarely succeeded in demonstrating mitotic plasma cells, and then only at the periphery of the nodule; certainly the number of them does not correspond to that of the plasma daughter cells. Usually where proliferation is marked, the mother cells occupy, in a thin layer, the outmost periphery of the nodule, and there succeeds to them, towards the centre, a broader ring of closely packed plasma cells, with large, vesicular, very granular, and deeply stained rings of protoplasm. Among these there now and again appear multi-nuclear plasma cells, as large or larger than the mother cells, but usually containing in their centre three or four flattened, facetted-looking, somewhat smaller nuclei. The form of these nuclei points to division by segmentation. But these are not lupus giant cells, we reserve this name for regressive degenerative elements, which are, in general, much larger.

At all events, whether an actual zone of proliferation of plasma cells exist at the periphery or not, when the disease has lasted any time, we always meet in the centre of the elementary nodules a remarkable change, very characteristic of tuberculosis. The previously

very granular, deeply staining protoplasm of the cells swells up, and thus the larger cubical plasma cells become rounded, the smaller ones show a broader ring of protoplasm, the specific granulation at the same time disappears, and the cells take on a homogeneous aspect. In the larger plasma cells the " homogeneous swelling " usually affects only segments of the cells, an end or a corner, while the peri-nuclear part of the cell body remains granular, and even continues to proliferate ; there thus develope small " giant cells." The nuclei resist homogenisation much longer than the protoplasm, and do not enlarge, and thus we meet with many paled and swollen cells, with well - stained nuclei. The margin of the cell always remains recognisable, even in cells which are converted into homogeneous balls.

In this homogeneous swelling we are not then dealing with a coagulative necrosis, nor with a cell dropsy, the cell substance rather remains solid, dry, and without vacuoles ; nor are we dealing with a mucoid, amyloid, hyalin, and certainly not with a colloid metamorphosis, whose refraction and staining are different. Either the granules of the plasma cells, drying up, are converted into more homogeneous, non-staining masses, something like the kerato-hyalin granules in cornification, or—and this appears to me the more probable—we have, in the homogeneous cells of the centre of the nodule, the expression of a direct combination of the granular plasma cells with a poisonous substance proceeding from the tubercle bacilli. The homogenisation usually affects smaller groups of (2—4—8—12) cells, and we find, in the centre of such groups, just as later in the giant cells corresponding to them, a few tubercle bacilli. Further, I was able to prove that tuberculin, *by shrinking* (removal of water), converted all the plasmomatic substances which survived into homogeneous, horny, yellow masses. Even before we had any idea of the albuminoid nature of tuberculin, I pointed out that this substance, which led to homogeneous swelling, could not possess basic properties, since nuclein was least affected by it.

As in all collections of cells which degenerate in groups and swell up, there is, immediately around them, a compression of the plasma cells, which guards them from the action of the poison, and consequently from homogeneous swelling. These relatively or completely intact cells consequently arrange themselves in rings or in semi-lunar form around such degenerated cell groups, and since their protoplasm and nuclei remain well stained, the elementary lupus nodule appears, in this second stage, to be composed of rounded, polycyclical figures, whose centres are occupied by the homogenised groups containing tubercle bacilli. This *figured* appearance of the cellular foci is quite characteristic of the circumscribed form of lupus, the elementary lupus nodule.

For its production two things are necessary—first, *an increase in volume of the degenerated cells*, but also, secondly, a *resistance to the increase in volume of the whole nodule*, an increased tissue pressure, which exists only in the circumscribed *encapsuled*, not in the diffuse, looser form of lupus. There is also homogeneous swelling, but no encapsulation of the cellular areas. Therefore we find this figured mosaic most typically developed in those areas which are embedded in perfectly healthy, firm skin, particularly of the extremities, in scars or in fibromatous tissue. Less clear but still distinct is it in circumscribed areas which are found immediately around, or which, as is often the case, appear in spots in the centre of a mainly diffuse, extensive lupus. Evidently, then, the tissue pressure in the areas is slight, the homogeneous swelling does not always attack the cells in groups, but often singly; but these then swell up all the more until they resemble large homogeneous globular vesicles, with nuclei, surrounded by a little granular protoplasm, lying on them. Here then we have in an individual cell a degenerating and a proliferating part, such as Weigert has assumed in the tuberculous giant cells in general. The nuclei of these large, solitary, homogenised cells also divide, but not so vigorously, and so, instead of dense colonies of small ones, we have only a group of three or four larger nuclei. Nevertheless we have here also a figuration of the whole area, for usually several adjacent homogenised cells have their nuclear pole directed to one side and the degenerated cell body to the opposite side, as if the degenerating influence had come upon them all from one side. Whether these cells in their further course remain distinctly isolated, or gradually unite by the common growth of their nuclear poles around the degenerated cell bodies, is a fact of little importance. Either may occur.

However the figuration of the cellular areas has developed, where it is present, the diagnosis of lupus may be immediately made, even where no giant cells are present, for in other plasmomata this form of degeneration has not been recognised.

The giant cell formation, which is the particular birthright of nodular lupus, developes on the base of the previous figuration of the area, and thus the third stage is introduced, the acme, beyond which there are only regressive changes of the whole area. For, to put it shortly, every lupus giant cell exactly corresponds to a homogenised group of cells with their ring-formed compressed surroundings, or to a group of cells all partially homogenised; in any figured area we may see how many giant cells it will later contain, into how many it will, under circumstances, break down.

Every lupus giant cell consists of two parts, a degenerative and a proliferative part, which—in contrast to certain other giant cells—

are juxtaposed, and are developed in relatively very different degrees. The former corresponds to the original group of cells which undergo homogeneous swelling, and contains in its centre all sorts of heterogeneous things ; tubercle bacilli, accidentally resistant whole cells, but in particular, remaining, resistant, only partially degenerated elastic fibres. This is especially the case in the large giant cells with 20, 40 to 100 nuclei, which lie close together in ring or cap form, embedded in cell substance taking the protoplasm stain. The degenerated part of the small and the tiny giant cells often enough corresponds only to the very much swollen cell body of one single or a few closely adjacent cells, and contains in the former case nothing, in the latter only occasionally heterogeneous contents, which always point to an after enclosure by non-degenerated, and liquefaction of degenerated cell substance.

Any one wishing to convince himself that the giant cells develope in mechanically different ways, but always from the same material of homogenised and swollen plasma cells, and by the same process of indistinguishable coalescence of homogenised cell substance, and their enclosure by nucleated, non-degenerated cell substance, should follow the fate of the elastic fibres in nodular lupus. In particular, the branched remains of the elastic substance often give to the giant cells which endeavour to surround them the most remarkable forms, and we see at the first glance that the view that all giant cells are uniform structures, corresponding to single cells, is untenable.

Often the giant cells are only seated on one elastic fibre, and thus several may meet, and, separated at their nuclear poles, may unite at the homogeneous pole. The same is shown by very powerful nuclear staining, which often demonstrates, inside the homogenised zone of very large giant cells, complete, hardly homogenised, nucleated plasma cells.

One has thus to regard the cell body of the giant cell, even in its homogenised parts, as living, and Friedländer has already recognized movements in it. There is no question of a necrosis of this part, because we find true necrosis of the cell in cutaneous tuberculosis, which is easily distinguished from this homogenised substance in the giant cells. While the protoplasm surrounding the nuclei of the giant cells may always be stained with basic colours, the homogenised protoplasm never is. It consists of a coarse but very regular net of dense substance and a homogeneous, faintly yellow, cloudy enclosure, and is thus very different from the simple homogenised plasma cell. As this structure increases in mass, as the giant cells grow at the nuclear pole, it suggests the common result of two opposing influences. The poison proceeding from the tubercle bacilli inside the homogenised part paralyses the protoplasm around it, entering into a dry homogeneous compound with it. In the neighbourhood of the nuclei this poisonous

action is not only paralysed, but the nuclear substance is stirred up to proliferate, and this, always accompanied by the escape of certain constituents into the protoplasm, regenerates the latter, so that, so long as the nuclear proliferation lasts, we never have complete necrosis of the homogenised section. But in this way both parts must continually grow, for every incitement to nuclear division on behalf of the poison adds new substances to the homogenised protoplasm, which are here retained.

Although I go so far with those authors who regard the giant cells as living, I would still not ascribe to the homogenised part any absorbing or secreting, assimilating or digestive power. The motionless tubercle bacilli are, from the commencement, enclosed in the giant cells in spite of their frequent multi-cellular development, or later imprisoned, like the equally immovable elastic tissue. The signs of degeneration and absence of staining power, which the latter show when they lie inside of or penetrate the giant cells, are no proofs of a phagocytic action of the giant cells, but are the results of the same poisonous action which has paralysed the affected parts of the cells. Indeed, knowing how very easily the elastic fibres are absorbed in every inflammation, their long resistance inside the giant cells is remarkable, for they may completely disappear in the neighbourhood of the vigorous plasma cells, and their persistence must be ascribed to the partial paralysis of the giant cells.

As a whole the lupus giant cell is a structure little uniform in its origin, but ultimately forming a uniform scheme, in which an excessively proliferating part is fettered to an over-nourished, but paralysed part—an example of the "neither dead nor alive condition," which even clinically distinguishes chronic tuberculosis of the skin, lupus.

The transformation of the circumscribed lupus plasmomata into a homogenised mosaic of cells, and finally into a group of giant cells, takes place mainly under the influence of two factors: tissue pressure and age. The more the areas swell, compress their surroundings, and thus become encapsuled, the more energetic is the transformation; and on the other hand, the areas of course contain more giant cells, the longer they last. A complete transformation into giant cells is very rare. There is usually a thin shell of well-stained plasma cells forming the margin from the healthy tissue.

In addition to angular remains of elastic tissue, mast cells are often enclosed in these degenerated areas, but they are rounder than usual and their granules less stained. They are less numerous than in diffuse lupus.

After its transformation into a collection of giant cells, circumscribed lupus may remain very long unchanged, if there is no external

irritation, particularly inflammation. I have examined cases which have lasted for decades, and found exactly the same appearance as in cases which had lasted for months. A balance is established between the action of the poison and the reaction of the skin; the tubercle bacilli have thrown up a wall around them, inside which they repose, latent but not dead.

2. *Lupus diffusus, radians.*

In lupus nodularis it is just possible to find an analogy between miliary tubercle of other organs, *e.g.*, the lungs, and the central homogenised parts of that form of lupus. Since, with a few remarkable exceptions (for example Baumgarten), these are regarded as caseated or caseating and as actual tubercles, one is led to regard the cellular periphery, the matrix of the centre, only as a reactive leucocytic wall, and thus to understand by "tubercle" of the lupus skin, not—as we should—the whole plasmoma area, but only its more or less large central zone of degeneration. That this error was widespread, was shown very clearly at the time of Koch's discovery of tuberculin. Koch rightly and cautiously spoke of a liquefaction of the "tuberculous tissue" of lupus after the injection of tuberculin. Since many began their histological investigation with the incorrect view that this was the degenerated centre of the lupus area, wonder was expressed at the persistence of the latter, in spite of the tuberculin injection, and the finer changes which actually took place in the matrix were over-looked. And further, it was evident from the description of authors and the very vague use of the name, epithelioid cells, even from the free use of this very indefinite and meaningless term, that there was no agreement as to what was the margin of the actual tubercle inside the lupus skin; indeed, previous to the definition and tinctorial isolation of the plasma cells, such was not possible.

It is therefore not to be wondered at that an important, because very frequent, form of lupus tissue, namely, the basis of the diffuse lupus, has up to now been invariably over-looked. Men always look for areas, like the tubercles of other organs, which are no doubt present in numbers in every nodular lupus, and regard everything else as non-characteristic. But since the discovery of plasma cells all this is altered. While the plasmoma in circumscribed lupus plays the main rôle as the matrix of the tubercle, diffuse lupus consists mainly of unaltered tubercular plasmoma. If we had to found the diagnosis of lupus on the zones of degeneration of tuberculous tissue, much of what we call lupus clinically, would not histologically be so. For there are often enough cases of lupus, especially rapidly advancing lupus of the

face, where no degenerated parts are found. The whole lupus then consists only of plasmoma tissue, and to regard this as not specifically tubercular would be absurd. In the comparison of this lupus with the more familiar Lupus nodularis we see the important rôle which, in every case, the plasma cells play in the formation of lupus. The *initial omnipresent and therefore characteristic tissue is the tubercular plasmoma*, and the question rather is: why, in a number of cases, the tuberculous tissue of the skin remains at this stage (lupus diffusus, radians), while in other cases it goes on, through homogeneous swelling, to giant cell formation (Lupus circumscriptus, nodularis).

In the description of this latter form, I have already pointed out the influence which the increasing pressure, always becoming greater in the encapsuled areas, induces on their degeneration. This degeneration is only present in limited degree or altogether absent, where the tubercular tissue is not encapsuled, does not form nodes, but extends radially in all directions into the tissue spaces (therefore: Lupus radians). There must be pre-existing differences in the texture of the skin, which cause this distinction, and the topographical and other differences between the two forms make the otherwise plausible assumption very probable, that a given degree of anæmia, dryness, and firmness of the cutis favours an encapsulation of the plasmoma. Under such favouring circumstances the infectious influence of the few tubercle bacilli does not extend far, and so the formation of plasmoma is not extensive, but in its limited space becomes more and more intense, up to complete disappearance of the original tissue, so far as the plasmoma reaches. If more intense poisonous action leads to swelling of the cellular area, the increase in size only induces compression, not a further splitting up and liquefaction of the surrounding tissue, and there gradually developes a capsule of thickened tissue around the area, which makes the extension of the plasmomatic change even more difficult, and thus shuts off the poisonous action from the surroundings.

But if from the commencement we have a more vascular, moister, looser skin, the absorbed poison makes its way over a relatively larger area of skin, the greater circulation of lymph constantly dilutes it, and thus we never have an excessive action of the poison. The result would be a more diffuse extension of the plasmoma, which streams radially in all directions in the lymph spaces, extends along the absorbing blood and lymph vessels, and presents as a whole a reticular new formation of cells with swollen knots. The action of the poison being less at each individual place, we do not readily get a total liquefaction of the collagenous tissue at definite points, and thus no formation of purely cellular, swollen and degenerating areas which

are sharply margined from their compressed surroundings and encapsuled by them. On the contrary, the nature of this form of plasmoma is to distend the lymph spaces of the cutis in all directions, to loosen it, and thus to advance unhindered and undelayed. One can thus better determine histologically than clinically whether the prognosis is favourable or unfavourable, whether the tendency is to encapsulation or extension.

The histological basis of the two main clinical forms I consequently find in the fact, that in the one the tubercular tissue compresses tangentially the surrounding healthy tissue, while in the other it breaks radially into it. Of course the cases are rare in which either form is purely developed. The most frequent are those pure forms of Lupus nodularis, such as were described in the previous paragraphs. In many cases we find around a central lupus area, of the nature of radiating lupus, a series of smaller encapsuled areas, or it is sharply margined at one side, while at the opposite it passes diffusely into the surroundings. This depends on the varying texture of the cutaneous tissue. The discussion of all the combinations of these two forms is as unnecessary as it is impossible. I shall only give shortly the description of the pure, diffuse, radiating lupus, such as is very frequently seen in the markedly erythematous cases on the face.

We find here, at the commencement, the plasma cells around the sub-papillary vascular net radiating in processes into the papillary body and outwards into the cutis, without anywhere forming rounded areas. Consequently the blood vessels are not compressed, but, as they run through the areas, retain their normal width or are even dilated. The plasma cells are mainly developed from the perithelium of the blood vessels, but also from all simple connective tissue cells, so that the plasmoma area has from the commencement the form of a net, whose thicker strands follow the vessels, the follicles and glands, while the finer ones surround the collagenous bundles. The latter, as well as the elastic fibres outside the plasmoma cords, are well preserved, so that, with an appropriate stain, there are evident two nets inside each other, that of the plasmoma which contains the blood vessels, and that of the collagenous and elastic substances.

We see that this arrangement is exactly the same as that of the cells in all weaker poisons, and shows nothing specific of tuberculosis. But as it advances, more and more collagenous and elastic islands are liquefied in the centre of the area, as the extending plasmoma advances. At the same time the vascular system is more and more involved, the capillaries being converted into plasmoma tissue. This takes place first in relation to the sub-papillary vascular net and in the papillary body, so that, at a second stage of development, a patch of plasmoma

extends from the epithelium to about the middle of the cutis, and sends off branches in all directions, especially downwards, which follow the vessels, surround the coil glands, and penetrate into the fatty tissue. If, at the first stage of development, the lupus area clinically resembles an erythematous spot, which only shows its tubercular character when the erythema is pressed aside, at this second period the lupus character is evident from the colour and translucency; only the border of the area is more hyperæmic and diffuse than in Lupus circumscriptus.

Inside the area there are at this time no evidences of degeneration. There are neither homogenised cells nor giant cells, and at the first glance it hardly looks like lupus. But as the area advances these appear, although more slowly than in nodular lupus. Evidently they require a greater mass of plasmoma tissue, left to itself, whose centre is widely removed from the nearest blood vessels. There then appear in the centre of the area a few homogeneous, swollen cells, and rows of them, corresponding to the streaky character of the original cell growth. A figuration of the cell masses does not take place in this looser form of lupus, or only at very limited places, and there is only a very scanty development of giant cells.

We have nothing to suggest the familiar scheme of tubercle, and yet we have before us a pure form of tubercular tissue. The signs of degeneration, so far as they are present, are exactly the same as in circumscribed lupus, only here the swollen cells in size, the proliferating nuclei in number, and the giant cells in growth, are less than there described. We have at most, in time, a broad pale zone in the centre of the whole area, containing a few giant cells.

In an interesting variation of this form of lupus the plasmoma is very feebly developed, so that even when of long standing there is no patchy combination, but the lupus remains stationary at the first stage of scattered, perivascular cellular infiltration. At the same time the hyperæmia of the vessels is unusually developed, and there is added to it a permanent, slight œdema of the papillary body, with dilatation of all the superficial lymph spaces. Clinically, this lupus resembles a persistent erythema. It is the form which Leloir has recently described under the name "*Lupus erythematoides*," and which, as this short sketch shows, has not the least resemblance, either histologically or clinically, to Ulerythema centrifugum, the so-called Lupus erythematosus (see the histology of Ulerythema centrifugum).

But very few cases of lupus diffusus are so simply constructed as this. The rich supply of blood favours the fact that inflammatory and hyperplastic processes of a peculiar nature almost always complicate it, especially hypertrophy of the epithelium, and that sero-fibrinous in-

flammation peculiar to the tubercular poison. But since these secondary processes on the one hand do not necessarily occur in Lupus radians, and on the other, although rarely, also complicate Lupus nodularis, we must consider them separately.

(a). *Epithelial hypertrophy in Lupus.*

A simple hypertrophy of the epithelium is one of the most frequent additional symptoms of lupus. The individual cells are much enlarged, their nuclei and nuclear granules multiplied. In spite of their enlargement, they stain as well or better than usual, which shows that the enlargement is due to a true hypertrophy of the cell. Consequently the inter-epithelial spaces are not dilated, and only moderately invaded by wandering cells, the pure uncomplicated forms of lupus are thus clearly distinguished from similar older syphilides; the epidermis does not suffer in the least from the tubercular poison, but is only stirred up to increase in volume and proliferation. Mitoses are regularly found in quantity in the prickle layer, and the horny layer is, as a rule, thickened or scaling.

The two main forms of lupus behave differently in regard to acanthosis. Above the solitary and agglomerated nodules of the circumscribed lupus, which press all the tissue to a side, there is no ingrowth of epithelium. On the contrary, the surface epithelium over such nodules is usually thinned. But where this mechanical factor does not act, directly at the side of the nodule, the epidermis penetrates the cutis in broad, branching ridges. In particular, the ends of the extremities are a favourite seat for the generally rare combination of Lupus nodularis with epithelial growth, for there the epidermis is normally very thick, and readily tends to grow, and, on the other hand, the very firm, relatively anæmic cutis greatly favours the encapsulation of the lupus. The epithelium then grows round the very superficial nodules, and sends further epithelial processes into the cutis, beneath their level. In time these deep epithelial ridges, which enclose the lupus nodules, cornify, and when the horny lamellæ have fallen out of them, they show a warped, papillomatous, warty surface. The papillary elevations on the fore-arm and leg usually all tend in one direction, for there the prickle layer, on account of the pronounced folds of these regions, grows obliquely into the cutis. The individual elevations are clothed with a thick horny layer, and a moderately thick prickle layer, which also partly penetrates through them, and contain a firm connective tissue process, furrowed off from the rest of the skin. In this, right up to the point, we find circumscribed plasmoma nodules with a degenerated centre, and giant cells, which, on account

of the epithelial growth, now come to lie above the level of the surrounding cutis.

Such is the development of the distinctly warty form of lupus, Lupus verrucosus, and of the slowly extending tubercular post-mortem wart (Verruca necrogenica tuberculosa). It is the most benign form of lupus, and almost always, especially on the fore-arms, heals in the centre, while it extends very, very slowly peripherally. Two factors favour its encapsulation; the firm anæmic tissue of the cutis, and the epithelial growth which leads to sequestration of the superficial nodules.

But the epithelial growth only produces such grotesque forms

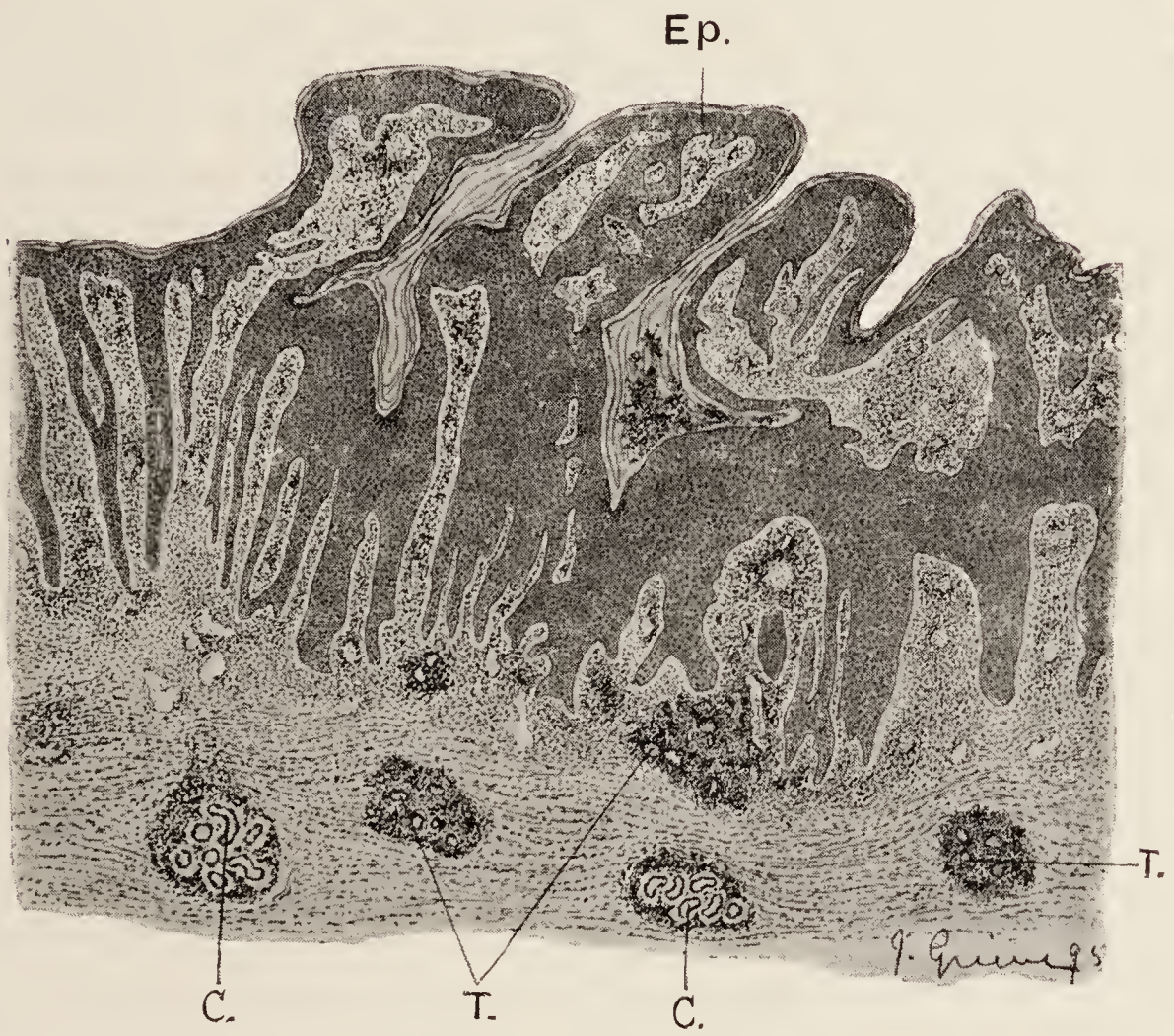

FIG. 24.—Epithelial Hypertrophy in Lupus.

Ep. Hypertrophied epithelium.
C. Coil glands dilated.
T. Tubercular areas with giant cells.
Other smaller darker areas are composed of plasma cells

under the above coincidencies. As a rule it only plays an important rôle, not in the circumscribed, but in the diffuse lupus, and even there, not clinically, but only histologically. It is easy to see that the epithelial growth aroused by the tuberculin in the lymph is almost the normal condition in the diffuse form, which is always washed to a certain extent by the poison. We meet very few cases of diffuse lupus

which do not show some signs of acanthosis. Usually the whole ridge net over the plasmoma is equally thickened, gradually increasing towards the centre. But further, in certain places, often in the centre, it grows deeply into the degenerated cutis tissue. In this we find a distinction between the epithelial growth in syphilitic and tubercular processes. The former are firmer, and firmest of all in the centre, the latter, both at border and centre, equally soft and yielding. Thus it is that the syphilitic plasmoma is so frequently enclosed by hypertrophic marginal ridges, while in lupus, broad epithelial depressions are present over the whole surface, and especially in the centre.

There usually are, in addition to a very broad ridge or a broad projection of the prickle layer, a number of fine, deeply penetrating processes. While the coarse depression consists of very voluminous cubical epithelium, the fine processes are composed of small, leaf or spindle-shaped, laterally compressed cells, which are, however, completely stained and therefore easily followed—another distinction from syphilitic acanthosis, where the split-up epithelium is badly stained and loses itself unnoticed in the depths of the skin. These fine processes often run through the lupus in the form of a net, and contain, in all their meshes, large, typical plasma cells and sometimes even giant cells, which are formed most easily, in diffuse lupus, in the parts surrounded by epithelium.

The larger epithelial processes frequently show scaly, compressed epithelial pearls and also horny pearls, as well as a few colloid degenerated globular epithelial cells and globular enclosed sections of them. They only contain wandering cells in moderate number.

The a-typical epithelial growths of Lupus diffusus are thus easily distinguished from ordinary carcimonatous growths, which are now and again present in long-standing lupus. In them the epithelial processes are firm and margined by cylinder cells, which are regularly arranged on the connective tissue, and not by epithelium which is laid flat on it, to say nothing of other differences. Confusion is more likely with the fine, extending processes of rodent ulcer, but no such combination has been described. Indeed we rather require a critical revision of the literature of lupus carcinoma to see whether it does not contain many cases of simple rodent ulcer, for this disease, at least in Germany, is, at the commencement, almost always confused with lupus.

The hair follicles share little in the a-typical epithelial growth, but they are often occluded, after their surroundings have passed into the lupus plasmoma; as are the sebaceous glands.

But the coil glands show peculiar and constant changes. At first we almost invariably find the sweat pores, the lumina of the ducts and the coils dilated; even to such a degree that cystic dilatations and even

spherical cysts develope. The former are most frequently found in the coils, the latter in the ducts. In most cases the epithelium is larger, but otherwise normal, in particular, normally stained. Secondly, the coils, in which the lumen is dilated and the epithelium enlarged, have a peculiar appearance. They are invariably closely surrounded by dense, large celled nodules of plasmoma, and embedded in collections of giant cells. In such cases there always arises the question, whether these giant cells have developed from parts of the coil or only from the surrounding plasmoma, which leads to a further question: can tubercular giant cells develope from coils?

Stimulated by the example of Baumgarten, I have long diligently sought for definite proofs of such a development, and only a year ago discovered a single example, though it was not beyond question. But recently I have discovered, in a lupus of the palm of the hand, a definite proof of the positive existence of such coil giant cells, and in almost every section all possible transitions. Therefore giant cells may be formed from the epithelium of the coils, all the epithelial cells running together, with disappearance of the lumen, into a spirally winding, solid, epithelial mass with many nuclei, mostly marginal but also central, quite distinct from the surrounding plasmoma, which may also contain giant cells. Then the epithelial mass degenerates "en bloc" in the centre, first with homogeneous swelling and then here and there in a reticular form, into an unstained, yellowish substance, like the giant cells of connective tissue. Ultimately these spiral giant cells are very difficult to separate from their degenerated surroundings. There appears to set in a subsequent warping of that part of the coil embedded in the plasmoma area, and in this connection the epithelial giant cells differ from the ordinary ones, for they are always sharply marked off from their surroundings, and are therefore always easily recognised. Further, I have only seen the outer end of the coil converted into giant cells, the rest of the gland was normal or dilated—hypertrophied.

All these epithelial changes of diffuse lupus produce no particular clinical appearance, and therefore do not give rise to clinical varieties (analogous to Lupus verrucosus). But they have, in addition to the histological, a great therapeutic interest, for the rapid and easy healing of operated lupus is mainly to be attributed to the tendency of diffuse lupus to deep epithelial growth.

(b). *Sero-fibrinous inflammation in Lupus.*

This also occurs mainly in connection with diffuse lupus and a profuse development of the vessels. Since acute inflammation and

suppuration of the tissue, with coagulated lymph and leucocytes, are no necessary attribute of every lupus, the question arises, whether cases in which they are found are to be regarded as pure uncomplicated forms. Since the discovery of tuberculin, we know that the constituents of the tubercle bacillus alone are able to induce a high degree of sero-fibrinous exudation in the neighbourhood of the lupus tissue, consequently, when it occurs spontaneously, it is always to be regarded as the action of the same poison. Exudation and crust formation are therefore characteristic, but not necessary reactions of the skin to the tubercle bacillus, and we are in the fortunate position that we can produce them experimentally in every desired degree. In this experimental inflammation we see that it developes all the more easily, and is all the greater, the more vascular the lupus. The diffuse form reacts most rapidly, but the inflammation may be artificially produced, even in the circumscribed, encapsuled areas, by larger doses, and still better by injection of the tuberculin directly underneath or into the nodule. If a powerful reaction has recently taken place, we find the blood vessels much dilated, the capillaries densely filled, now with white, now with red blood corpuscles, and the whole surroundings of the lupus injected. According to its composition the capillaries penetrate more or less deeply into the lupus. The most striking appearances are seen in the epidermis, which is converted by the exudation into a collection of serous vesicles. At the border of the lupus, it may be seen that this change commences entirely between the cells, the lymph spaces are enormously dilated, and there are formed a number of tiny, interepithelial, serous spaces, margined by compressed epithelium; further, towards the centre of the lupus, the epithelial cells undergo primary degeneration, their protoplasm completely liquefies, and then coagulates into a delicate net of fibrin; in places there is reticular degeneration proper—*i.e.*, partial instead of total colliquation of the internal cell substance. These elementary vesicles run together on different parts of the surface, to form large bullæ, filled with serum, fine fibrinous coagula, and a considerable number of leucocytes. The whole of the epithelium thus altered then dries up into a loose, thick, coagulated crust, which is at once raised by the after growing epithelium.

Especially striking here are two things: the relatively small number of leucocytes in the epithelium, in view of the enormous dilatation of the lymph spaces, and the limitation of the exudation to the surface epithelium, while the epithelial processes, usually extending deeply in diffuse lupus, are hardly affected. This last evidently depends on the distribution of the dilated capillaries mainly at the surface of the lupus, while the epithelium inside is further removed from the vessels. Thus the saturation of the lupus plasmoma itself

is limited to an interstitial œdema, which, however, in high degrees of inflammation, may certainly give to the tissue a general spongy character. The regions containing plasma cells are more affected than the zones of homogeneous swelling and giant cells. The plasma cells are diminished in size, their granular cell body has liquefied and stains less, while the nuclei retain their power of staining. The cells now lie loose in the distended meshes of the connective tissue, and thus the spongy character developes. Here again the moderate emigration of leucocytes is remarkable. No doubt we find wandering cells everywhere in the tissue, where they are not normally found in lupus, but their number has absolutely no relation to the great quantity of serous, often sanguineous exudation which causes such severe mechanical effects; there is never any question of suppuration. But in studying this question we must avoid simple nuclear stains, which mask the differences between all forms of cells.

In contrast to the simple liquefied plasma cells, those giant cells and plasma cells, which are already homogeneous and swollen, apparently undergo no change. They are more isolated from their surroundings by the œdema, but both cell substance and nucleus show the same size and stain as before. At most a few leucocytes wander in between them and lose themselves in the interior of the giant cells, where they are found along with elastic fibres and other enclosures.

Altogether, then, the acute inflammation caused in vascular lupus by an excess of tuberculin leads to a saturation with serum, which coagulates in the œdematous cutis, and especially in the liquefied epidermis, but does not lead to suppuration, liquefaction, or general necrosis of the lupus tissue. In addition to the œdematous swelling, the most important external symptom is the rapid formation of thick, loose, coagulated crusts. Microscopical examination shows that these consist mainly of horny masses, with thick wedges of fibrin and a moderate number of leucocytes between them. Since these cases are mostly of the diffuse form, in which the epithelium has grown vigorously into the cutis, when the crust is removed only small parts of the cutis are laid bare.* This is seen at once on sections of the crusts, as well as on those of the whole skin. At those points where the apices of the papillæ, which have remained between the epithelial depressions, have gone with the crust, we find extravasations of blood and whole coagulated blood capillaries embedded in the under layer of the crust. But this punctiform baring of the cutis justifies no one in speaking of ulceration as the result of this inflammation; for that, suppuration or

* Only in anæmic, encapsuled lupus nodules, the reaction induced by tuberculin leads to the elevation of considerable stretches of the whole epidermis, along with the crust. But even here there is no suppuration.

some other liquefaction of the cutis is necessary, which is not present here. The whole cleansing power of the acute inflammation does not then go beyond a *deep exfoliation*; it is neither a slow liquefaction, nor a rapid enucleation of necrotic lupus tissue; the latter is only rarely present in extreme cases, in which, from complete stasis, the skin becomes gangrenous.

But the acute inflammation has, in certain definite but very limited spots, a necrotic action, though unfortunately only where there is least chance of absorption or throwing off of the infection—namely, in the centre of a few encapsuled plasmoma nodules. It is therefore not on account of its practical significance, but of its theoretical importance, that I briefly refer to this point. The fact has not been over-looked, but has not got the attention it deserves, because the view is very widespread that in lupus, as in other forms of tuberculosis, true necrosis is common. But this is an error, and we shall see in the description of scrophuloderma, that primary and secondary tuberculosis of the skin differ in this very point. The nature of this central necrosis in lupus will be considered there. Here it is sufficient to note that after Koch's injection, in the centre of a few plasmoma nodules, rarely in the centre of unencapsuled diffuse plasmoma masses, there is complete obliteration of the cell structure, the homogeneous cells being converted into a homogeneous mass, containing nuclear remains. This punctiform necrosis of already degenerated masses has not the practical result which Koch had in view, but it at least corresponds exactly with his first theoretical suggestion, that degenerated masses would become completely necrotic after the injection of tuberculin.

I have placed the acute inflammation after tuberculin, first, for it supplies us with means of properly estimating the ordinary chronic inflammation. Lupus crustosus is the same, only in a modified degree, as that just described. We find crust formation most frequently above the diffuse form. While those parts of the lupus which are more deeply embedded in the cutis show no change, the plasma cells in the upper part are not so well formed, the tissue between them is œdematous, here and there spongy, and the epidermis above is also œdematous, contains inter-cellular vesicles, and terminates in a more or less thick, fibrinous crust. Here also comparatively slight emigration of leucocytes is present, although they completely fill the capillaries in limited areas. In this chronic form of inflammation we never have a blood-shot crust penetrating into the papillary body, complete spongy loosening of the plasmoma mass, or punctiform necrosis of individual encapsuled plasmoma areas.

Clinical observation then compels us to recognise in the crusted lupus no exulcerated lupus; the whole inflammatory process, even

clinically, is much more related to the moist forms of Eczema than to the suppurating processes of Furuncle and Impetigo, and the complete analogy between the crusted lupus and lupus after the injection of tuberculin, shows clearly that the histological appearances of the former are just as I have described them, for the objection that an *increased* inflammation might now and again lead to direct suppuration of the lupus is invalid, in view of our familiarity with the acute results following the injection of tuberculin. We know that the most powerful action only leads to an excessive sero-fibrinous inflammation, never to suppuration. Therefore the domain of Lupus exulcerans, Lupus exedens, must in practice be very much limited. Most of the cases are simply examples of *crusted lupus.*

(c). *The fibrillary sclerosis of lupus, the tuberculous fibroma. Lupus scleroticus; Lupus elephantiasticus.*

The hypertrophy of the collagenous tissue, which complicates many cases of lupus, has, in contrast to the inflammatory conditions just considered, which often favour the extension of the tubercular process by dilatation of the lymph spaces and the removal of part of the plasmoma, an influence not completely curative, but nevertheless limiting. In this relation it is allied to the other progressive changes of the skin; plasmoma formation and epithelial growth, but of these it most surely leads to a temporary arrest of the infectious process. As the inflammation proceeds from the vessels, and the acanthosis from the surface epithelium, the sclerosis also has its definite point of origin, namely, the normal connective tissue, surrounding the plasmoma nodule or the diffuse plasmoma. The plasmoma is never converted locally into a fibroma, the latter always grows into the former, and finally largely replaces it.

In order rightly to understand the nature of this new formation, we must study the connective tissue in the neighbourhood of lupus. Here we always find progressive changes, certainly not yet in the collagenous tissue itself or in the elastic tissue around it, but in their mother tissue, the enclosing connective tissue cells. With a good protoplasmic stain, which also stains the plasma cells, we see that these no longer have the ordinary spindle formation, with a few fine accessory processes, but present large, protoplasmic and branched forms. They are well named "spider cells," so many processes do they "spin" in all directions, anastomosing with the neighbouring cells. The eye gradually gets used to following the differently coloured fibres, and we see that the collagenous substance is already surrounded by an unusually dense protoplasm net. A proper elastin stain then shows that the

fibres neither coalesce with the protoplasmic fibres nor pass into them, although they lie directly on them.

According as these protoplasm threads are slightly or greatly swollen, they pass suddenly or gradually into the body of the spindle cells; the broad processes may be called the "wings" of the spider cells. More important than a discussion of the very different forms of the cell, is the description of those parts which are constant. As such I would mention: a very large, almost always oval nucleus, with little chromatic substance and several small nuclear granules, which are now and again replaced by a mitosis, a finely granular, deeply stained protoplasm, which usually occupies the bases of the cell processes, and is limited to them, or more rarely fills most of the cell, and finally a frothy, faintly stained protoplasm, which forms the chief constituent of the cell, and often extends into the thicker processes. This frothy part of the protoplasm evidently contains two substances, of which the one, showing small compressed vacuoles, does not stain with basic colours, while the other, a spongy and less abundant substance, stains in the same way as the finely granular remains of the cell. By this predominance of the little stained, frothy cell substance, the darkly stained plasma cells are much more apparent than the very large spider cells.

Wherever the surrounding fibrillary tissue grows into the plasmoma, tongue-like processes always advance from these spider cells towards the lupus area. Thus the spider cells are constantly multiplying and diminishing, although not to the calibre of the ordinary spindle cells, in proportion as new collagenous substances appear between them. I have not yet obtained the proof that the latter develope directly from the spider cells, although it is more than probable. The whole process is something like this:—The protoplasmic net all around, and penetrating even the lupus itself with fine spindle cells and their processes, thickens at its margin by mitotic division, and in some way separates young collagenous tissue. I can only say that, from my observations, the plasma and mast cells never have an active share in this process, but are only enclosed passively in the new-formed fibromatous layers, and thus take on a cylindrical or flattened form.

The newly-formed collagenous tissue differs from the originally present, healthy fibrillary tissue of the cutis, in three main factors. It never consists of bundles crossing each other in rhomboidal meshes, but it always grows in horizontal layers, parallel to the surface, and therefore shows in all sections, almost horizontal, only slightly wavy bundles. This is the result of the total disappearance, under the influence of the plasmoma formation, of the old connective tissue bundles and the guiding vessels.

Then the tuberculous fibroma never developes elastic tissue,

although it may encapsule the remains which have been spared by the plasmoma.

Finally, this tissue is penetrated by a large, more protoplasmic net, which, instead of ordinary spindle cells, contains cylindrical and biscuit-like, flat cells, with numerous processes. Collagenous and cellular layers lie so regularly one above the other that vertical sections of a tubercular fibroma recall the appearance of a voltaic column.

The abundance of protoplasmic substance shows us that we are not dealing with a definite scar. With this harmonises, on the one hand, the reaction which the injection of tuberculin induces on the tissue, as on the plasmoma of lupus, and on the other, the further course, which may be in three different directions. Either the fibroma simply continues to extend, after taking up a part of the plasmoma; there then develope keloid-like, red swellings on the surface, or moderately hard thickenings, deeper down, *e.g.*, in the whole thickness of the lips, cheeks, &c. Or the protoplasmic part of the new growth gradually diminishes in favour of the collagenous; there then form, especially on the face, very hard new growths, which have been named *sclerotic lupus;* many cases of elephantiastic lupus of the legs come under this category. Or finally the lupus fibroma is converted into the *definite lupus scar.*

The prominence of the lupus fibroma always indicates an arrest in the extension of the plasmoma. This is the way in which nature heals lupus, *e.g.*, in the benign form of lupus veruccosus. If, commencing with the florid lupus, we review the small nodules up to the stage of healing, it is evident that the ingrowing connective tissue in most cases first takes up, in its horizontal layers, only the outer zone of plasma cells, so that, at a definite point, the areas of homogeneous and giant cells lie naked in the fibromatous tissue. In other cases the lupus nodules diminish as a whole, so that the diminished, homogenised centre is surrounded by a thin ring of plasma cells. Possibly this indicates that the homogeneous centres may not only be directly absorbed, but often in those cases, where the outer zone of plasma cells disappears under the influence of the fibroma, possess the power of a sort of restitution, into the form of deeply-stained plasma cells. Finally, at the healing margin of the plasmoma, the isolated nodules have completely disappeared.

It is less easy to follow the advance of the fibroma in diffuse lupus, for here no firm walls surround the lupus tissue, and the fibrillary substance has a free course in taking the place of the plasmoma. Since the original tissue, with its blood vessels, is not so completely absorbed in this form, and may partly direct the new

formation, the fibroma here is less regularly horizontally arranged; horizontal and vertical lines cross each other. The progressive forms of lupus react, even if all the plasmomatic tissue has disappeared, to the injection of the tuberculin, they liquefy under its influence, and thus show their *tubercular nature;* it is otherwise with the regressive form, the lupus scar.

(d). *The suppuration and liquefaction of Lupus.—Lupus exulcerans, Lupus vorax, Lupus phagedænicus.*

After the limitation of the definition of "*Lupus exuleerans,*" given on pages 590, 591, it is difficult to say what should be the use of this name in future. By exulceration we usually understand a suppuration of the skin, and since such is altogether foreign to typical lupus, there arises the question whether there is a secondary suppuration, induced by a mixed infection, which leads to the ulceration of lupus. The existence of such a mixed infection is not very probable on clinical grounds; for although the lymph spaces of the epithelium, and even of the cutis, open externally, we never have the appearances of typical suppuration of the skin (Impetigo, Sycosis staphylogenes, Furuncle). To me it almost appears as if the lupus skin, like the syphilitic, possessed a sort of immunity against pyococci, for I have sought for them in vain, in sections of very many lupus cases, even where there was great secretion, crust formation, and suppuration of the epidermis. I am very doubtful, then, whether such a mixed infection occurs; at all events the action of pyococci upon lupus tissue has not yet been proved.

But an ulceration of the skin may have other external and internal causes. The rare cases described as *Lupus vorax, Lupus phagedænicus,* in which large areas of skin, especially on the face (lips, nose, eyelids, cheeks), are, in a short time, totally destroyed by lupus, seem to show that the tubercular poison, after it has first induced a cutaneous reaction like ordinary lupus, may, under ordinary circumstances, also cause a rapid liquefaction of the skin. But as to how this occurs there is as yet no anatomical explanation. It is either a sort of phagedæna, such as may affect the syphilitic initial sclerosis; consequently a secondary infection of unknown nature, which can eventually replace the first infection. Or the cases are to be explained like the destructions in "galloping Syphilis," that is, they are due to a specially strong, individual idiosyncrasy of the tissue to the influence of the poison. Such would be evident in lupus, histologically, by a widespread liquefaction of the inter-cellular substance.

Whether the grounds which cause the sudden breaking down of

the lupus tissue are external or internal, they must give evidence of their presence by definite anatomical changes, and be of another nature than those just described, which are typical of the formation of lupus.

(e). *The absorption of Lupus.—Lupus resolutivus.—The lupus scar.*

Neither in the spontaneous healing of lupus nor in its disappearance under the chemical influence of drugs, have we to do with a simple absorption of the cellular infiltration. Scarring always takes place by the formation of a fibrous tissue, which grows between and into the cellular areas, partly replacing them, partly causing their disappearance by compression. The mass of the fibroma may be very small compared to that of the plasmoma, and we estimate the "beauty" of the scar by the small amount of fibrous tissue it contains. Lupus of the extremities, especially of the verrucous type, if left to itself, tends to heal with very little fibroma formation, and almost ideal scars. But such cases of *Lupus resolutivus* are rare. In most cases the lupus scars are marked by fibromatous processes, have a streaky appearance, and it is by no means easy to say, with certainty, whether the lupus has disappeared, and given place to a definite scar. We have in tuberculin a remedy which often enough demonstrates reacting, *i.e.*, lupus tissue in such apparent scars, and warned by this, we cannot be too careful in the histological diagnosis of the true lupus scar. Where we still find, in lupus scar tissue, small collections of plasma and giant cells, we have of course lupus tissue, and not a perfect scar. But even where all the cellular areas have disappeared, and only a dense hypertrophic, elastin-free, collagenous tissue in regular layers occupies the place of the cutis, it may still, measured by the tubercular reaction, be lupus tissue, and in such cases better methods of investigation would no doubt detect the few remaining bacilli, to which the reaction is due. It is consequently very difficult to diagnose lupus scars in all such cases where we have not a thin skin, as free from fibromatous processes as from cellular areas. Further investigation must show whether this quality of the foci only, guarantees the healing of lupus, for it is almost as easily demonstrated clinically as anatomically. Absolute certainty would be given, even in thicker skin with fibromatous processes, by the discovery of young elastin between them, as well as a new arrangement of the collagenous tissue in the lines of tension of the skin.

II.—Scrophuloderma, Secondary Cutaneous Tuberculosis.

Tuberculosis of the tissues lying directly under the skin, especially the lymph vessels and glands, almost always extends, in time, to the

skin, and produces appearances which are very different from those of typical tuberculosis of the skin, lupus. The skin is at first only œdematous and doughy, then becomes immovable, coalesces with the under-lying tubercular tissue, and participates in the fate of this latter, either extending over the level of the healthy surroundings, in the form of soft, sharply margined, bluish-red swellings, or, becoming united with the surroundings, thins them, and bursts. The brown, translucent colour, which is characteristic of lupus, only rarely appears as a brownish staining of the red parts, where liquefaction goes on slowly, and the dry tuberculisation of the skin extends everywhere to the surface. It is even then always more diffuse than in lupus. The circumscribed tubercular areas, which appear over incised and healed tuberculous glands, have arisen primarily from the inoculation of germs in the cutis, and are etiologically, clinically, and histologically, lupus. The tubercular degeneration of the skin, caused by secondary infection from within, is always distinguished by the complete destruction of the skin ; in distinction to lupus, the tissue may be completely and permanently shelled out from the healthy surroundings.

Since these cutaneous manifestations are only secondary to more important affections of deeper tissues, they have not received attention corresponding to their frequency—secondary tuberculosis of the skin is very much commoner than primary—and have usually been described as " scrophulous " inflammation, " scrophulous " abscess, and " scrophulous " gumma. We know now that all these appearances are really tubercular. But as we see that the clinical differences from lupus correspond to definite histological ones, and that they declare themselves by the secondary nature of the skin affection (?), it seems quite desirable to retain, for this form, the already adopted special name, *Scrophuloderma.* It must, however, be more sharply defined than previously, and include *all secondary tubercular affections* of the skin. There come under this head all those changes of the skin, which the fistulæ from tubercular bones, tendon sheaths, joints, bursæ, lymph glands and anal fistula present at their openings, and all those which are induced by the constant saturation of the cutis with tubercular poison, produced in internal tubercular areas.

Of course we have now and then transitions of scrophuloderma into lupus, secondary into primary cutaneous tuberculosis. Indeed, tubercular lymphangitis and resultant " tubercular gummata " may even develope from a lupus, and thus show the general relation of all the varieties. But these are the exceptions ; as a rule, the clinical distinction of the two is easy.

Scrophuloderma is best divided clinically, according to its seat, into *subcutaneous* and *cutaneous* forms, and further, according to the

different degrees, into *nodular, nodose, softening* and *gummatous.* The subcutaneous scrophuloderma, which corresponds to the course of the absorbing lymph vessels, has a cord or nodular form, is at first movable between the skin and fascia, and then unites with the former; the skin then thins and liquefies, and the moderately firm nodule gradually attains a fluctuating, abscess-like character, finally bursting, and leading to a flabby ulcer with indolent surface (Gumma tuberculosum subcutaneum). More rarely it developes in time into a *cutaneous* scrophuloderma of softer, more doughy consistence, and both are represented by bluish-red nodules and cords, which may last an indefinitely long time, but eventually, perhaps accidentally (*e.g.*, injection of tuberculin), or spontaneously, soften and rupture (Gumma tuberculosum cutaneum). Sometimes without any distinct subcutaneous scrophuloderma, a *cutaneous* one developes and usually extends, not in cord-like circumscribed fashion, but more flatly, is of a duller, brownish red colour and softer consistence, and is gradually elevated, with thickening (not thinning) of the skin, into a spongy, fungoid, not distinctly margined, flat tumour. It shows less tendency to gummatous softening than the first form.

Finally, we must note a very frequent form of scrophuloderma, *the tubercular cutaneous fistula*, discharging tissue debris from an internal focus. Here the surroundings show, in greater or less degree, according to the size of the fistula, the type of the cutaneous scrophuloderma, a somewhat transparent, brownish or reddish colour. The margins of the openings are usually lipped, pale blue and transparent. From the opening comes a thin fluid containing necrotic tissue, nuclear fragments, and a few pus cells.

The *subcutaneous scrophuloderma* owes its origin in almost all cases to a tuberculosis of the lymphatics of the subcutaneous tissue. The extension of the nodules and cords in the course of the lymph vessels, between a lupus of the finger or hand and the nearest lymphatic glands, clinically demonstrates this mode of origin. Positive anatomical proof is certainly difficult, since in almost all cases, however soon they are excised, the lymph vessel is completely taken up into the tubercular nodule, and no longer recognisable. But the probable point of origin may always be surmised, by exclusion. For the larger subcutaneous veins are pressed aside and evidently only secondarily affected, and the arteries are perfectly free. Further, in a few sections, I have been fortunate enough to recognise larger lymph vessels at the periphery of the smallest subcutaneous nodules, running towards the centre of the cellular infiltration and losing themselves in it.

The structure of these nodules I can give in a few words, after the thorough description of lupus, for, at the commencement, we are deal-

ing here with a plasmoma of exactly the same character as in lupus. It is remarkable that this is almost always of the circumscribed nodular form. We may find a series of smaller nodules, which have a border of large plasma cells, grouped around a larger, oval or cylindrical nodule, seated in the upper part of the fatty tissue, more rarely at the margin between this and the cutis, widespread in the fatty tissue, but not so much so in the region of the coil glands above. These are succeeded by a more or less broad wreath of small plasma cells, and in the centre, by a typical figured mosaic of paled multi-nuclear cells, or numerous giant cells. The further the growth is removed from the primary area of tuberculosis and the nearer it lies to the lymph glands, the deeper is it embedded in the fatty tissue and the more purely subcutaneous. Clinically, it looks in such cases like an enlarged lymph gland, but is seen histologically to be only an affection of the hypoderm, around a large subcutaneous lymph vessel. The fatty tissue immediately around the growth is completely normal; only when the panniculus is attacked do the fat cells atrophy and give place to large spindle cells, and later to plasma cells.

This ingrowth usually takes place diffusely, the new formed cells following the capillaries of the fatty tissue and embracing the individual fat cells with ever broader processes. As these gradually disappear, the fatty tissue is replaced by tubercular tissue, in which a few isolated islands of fat may persist. The nearer the central area the original lymph vessels, the more entirely does the tubercular tissue consist of plasma cells and their derivatives; further out, more spindle cells and newly formed collagenous tissue appear between them; here also, as in lupus, the tubercular fibroma grows mainly from without, between the tubercular plasmoma nodules. But there are the following differences due to the arrangement of the fatty tissue: this is penetrated by powerful collagenous septa, which send off, laterally, smaller septa between the fat cells. Thus arises the areolar structure of fatty tissue; the individual fat lobules have usually their own capillary supply. The spindle cell growth which introduces both the plasmoma and the fibroma formation, always takes its origin from the septa, and extends towards the centre of the areolæ. The plasma cell formation immediately follows, but only immediately around the blood capillaries. Now, where the influence of the poison is great, around the main areas, the plasmoma formation permeates the whole areola and prevents the fibroma formation. At the periphery of the new growth the plasmoma formation is less, the fat cells are permeated and replaced by tubercular fibroma, and finally only small bands of plasma cells, corresponding to the few remaining capillaries in the larger septa, indicate the margins of the original areolæ. Here, as in

lupus, the capillary system disappears, as the plasmoma and fibroma increase.

And further, the nature of this permeation of the fatty tissue explains the tendency of the plasmoma to the *nodular* form, for the individual areas, from the commencement, develope inside limited spaces, therefore under increased pressure. Thus we have very soon figuration of the areas and giant cell formation.

So far subcutaneous scrophuloderma exactly resembles nodular lupus. But from this point the development extends beyond that of lupus, for there now takes place regularly, in the centre of the plasmoma areas, that *necrosis*, which is seen in lupus only exceptionally and in very limited extent (in ulceration of the surface from injection of tuberculin, in the centre of the plasmoma and irregularly after caustics).

This necrosis, which is characteristic of scrophuloderma, appears in two different forms, which are found together on almost every section; a *dry* (direct) and a *moist* (indirect) form. The saturation with tuberculin, which lies at the bottom of the necrosis, affects the dry, a-vascular plasmoma, and has then the same simple effect as when a piece of fresh plasmoma tissue is allowed to die in Koch's tuberculin. All the cell protoplasm loses its granulation, and becomes cloudy and homogeneous, while the form of the cell is retained; the slight remaining inter-cellular substance is also preserved. Then all the protoplasmic and inter-cellular substance runs together into a cloudy homogeneous mass, which takes acid instead of basic colours. This contains very numerous remains of all sorts of nuclei, for the necrosis spares the nuclei for a long time, if not altogether. Under the influence of the saturation with tuberculin, a number of connective tissue nuclei shrink, but stain more deeply; they remain round or break up into more or less rounded fragments. If the latter remain united they often resemble the clover or trifoliate leucocytic nuclei, but they are in general clearly distinguished from them by their round form and usually greater size. We see here, how little the chromatin of the nuclei, as a rule, suffers from necrosis, for close to the margin of the necrotic tissue, now and again in completely homogenised cells, we sometimes find one showing mitosis, and in the central, completely necrotic zone, there are a number of nuclei with deeply stained projections and constrictions, which must be regarded as irregular mitoses. This is certainly no necrosis with primary nuclear disappearance, which might be identified with coagulative necrosis. Giant cells and multi-nuclear cells gradually pass so completely into the necrotic region, that they can no longer be distinguished as such. For a time they may be recognised by the closely lying nuclear fragments.

In contrast to this direct, shrinking necrosis, there developes in all those parts of the plasmoma which still contain open blood capillaries, under the influence of the saturation with tuberculin, first a *reaction of this nutrient apparatus*, which is accompanied by an œdematous swelling of the plasmomatic tissue. But this modified tissue passes later into a shrunken, necrotic tissue, a process which I distinguish as the indirect or moist form of necrosis. The swollen plasmomatic parts show capillary loops filled with leucocytes, widely separated, large, deeply-stained plasma cells, and between them very large spindle and spider cells in a very loose, collagenous tissue, permeated by large lymph spaces, altogether the appearance of ordinary tubercular granulation tissue. They pass, towards the centre, into the necrotic zone, the abundant succulent intermediate tissue shrinking, the granulation of the plasma cells disappearing, and the cell nuclei being retained completely, or in the form of deeply-stained fragments. These necrotic parts are distinguished from the directly necrosed ones mainly by their characteristic but always moderate amount of leucocytes, of which, in the centre, only the nuclear fragments remain.

As a whole, the necrotic zone int he centre of the scrophuloderma has the form of a cylinder or a slab, with or without processes; in very small areas it is more spherical. The direct, dry necrosis always encloses a regularly rounded, purely central area, whose margin is parallel to that of the whole nodule. These "caseous" areas are just the same as the circumscribed necroses in the centre of the nodules in the nodular form of lupus, after the injection of tuberculin. But more varied appearances are provided by the indirect necrosis, with precedent formation of tubercular granulation tissue. Here the vascular parts of the plasmoma send tongue-like processes towards the centre. The caseous centre thus has projections, which penetrate like wings into the vascular, looser parts. These appearances recall the form of the partial, small, irregular necroses, which are sometimes caused in the centre of diffuse lupus by the injection of tuberculin.

In all cases of scrophuloderma, both forms are found in different parts of the nodule, and the caseous, partly confluent, partly areated parts have therefore a very irregular form. But they always occupy the centre of the whole nodule, and therefore certainly correspond to the original lymph vessel which contained the tubercle bacilli, and its immediate surroundings. With a good protoplasm stain with alkaline methyl blue, it stands out greenish blue from the bluish violet of the peripheral plasmoma and from the faintly-stained transparent tongues of œdematous granulation tissue.

The so far centrally caseated scrophuloderma need not be clinically evident as anything more than an uncoloured, soft, subcutaneous nodule.

But the skin over it is often reddened, and pressure with a glass shows the deep-seated plasmoma shining through as a yellowish translucent spot.

The different methods of extension of the process in the cutis lead to the above-mentioned clinical forms. In some cases the deep necrosis increases very much, and affects the greater part of the plasmoma, so that when it extends to the cutis the central necrosis attacks that also. Then the skin naturally liquefies, becomes thinned over the swollen scrophuloderma, simply serves as the point of rupture, and its structure is hardly evident. We have then the *subcutaneous tubercular gumma* (Besnier). In other cases the necrosis is more limited, while the plasmoma slowly but steadily extends to the skin. This then takes on almost the structure of lupus, but swells up much more, the slowly advancing necrosis continually giving rise to a multiplication of the cells and to an œdematous swelling, before complete necrosis of the skin sets in. This presents, along with the hypoderm, for some time, a continuous spongy mass, which only needs some injury in order to soften and break down superficially. Thus developes the *cutaneous tubercular gumma.* Finally, though much more rarely, we have, without any previous distinctly-margined, subcutaneous nodule, a diffuse plasmomatic degeneration of the skin immediately over the tubercular lymph vessel, bursa, etc., which resembles lupus the more, the nearer it is to the surface.

In all cases the secondary tuberculous degeneration of the skin takes a definite route upwards, the first stage of which is formed by areas of plasmoma, surrounding the coil glands, along with the papillary parts of any lanugo hairs present. From here rows of plasma cells extend upwards along the coil ducts, hair follicles and muscles, through the cutis, and, in the sub-papillary layer, along all the capillaries. On this coarse meshed, reticular permeation of the cutis with plasmomatic cords, there immediately follows a finer one, all the connective tissue cells swelling and plasma cells being formed in the centre of the proliferating collections. The plasmoma of the skin, thus produced from below, is consequently exquisitely diffuse, though not to be compared with the diffuse form of lupus, for the plasmomatic cords are never so thick as there. Here also the tubercular poison induces proliferation of the epithelium, but usually only a moderate general thickening and lengthening of the ridges.

Thus the change of the skin, which is clinically evident as yellowish red or reddish brown staining, without swelling, may last for an indefinite time, until, acutely in the subcutaneous gumma, chronically in the cutaneous, a complete transformation of the cutis into plasmoma sets in. The collagenous bundles now first partially liquefy from

below upwards, elongated or spherical plasmomatic areas appear in place of the original plasmomatic net, and with them the familiar products of degeneration: homogeneous, swollen, multi-nuclear cells and giant cells. But it does not stop here; true necrosis follows the plasmomatic degeneration upwards. In the subcutaneous rupturing forms, it is limited to the centre of the area and attacks all the constituents of the skin; in the more persistent cutaneous gumma, it appears more scattered among the individual areas of plasmoma, and in this form there is a tendency to the development of the œdematous intermediate stage of true tubercular granulation tissue, to which cutaneous scrophuloderma owes its spongy consistence.

This form of cutaneous scrophuloderma is the more frequent. Wherever the panniculus is very feebly developed, the lymph vessels, bursæ, bones, tendon-sheaths, &c., running almost directly between fascia and cutis, a diffuse plasmoma of the skin is formed more rapidly and more superficially, closely resembling lupus, although its ultimate fate is different.

The *tubercular cutaneous fistula*, both anatomically and clinically, resembles the subcutaneous scrophuloderma, which penetrates the cutis. On section it shows a complete central necrosis in the form of a cylindrical cord or tube. Then we have, proceeding outwards, first a zone of degenerated plasmoma, permeated by fibromatous processes, and then a still broader zone of a reticular, diffuse plasmoma, which gradually passes into the healthy surroundings. At the edges, the epidermis is usually prolific and the plasmoma œdematous. The *cutaneous fistula is therefore a serophuloderma, growing cylindrically through the skin*, and is only distinguished from the other forms by the fact that the necrosis is more extensive in the centre, and at the borders of the fistula. Every recognisable trace of protoplasm and inter-cellular substance is lost in the necrotic mass, most of the nuclei have disappeared, and only elongated fragments of the chromatic substance of a few connective tissue cells and leucocytes are enclosed in it. This is, of course, due to the fact that the banks of the fistular canal are constantly in contact with fresh necrotic masses from the primary area, and the necrosing substances which they contain.

The peculiarities of those tuberculoses of the skin, grouped under the name scrophuloderma, may all be ascribed to the fact, that the poisoning of the skin is not, as in lupus, due to a few bacilli which have penetrated the skin itself, but to collections of bacilli, which have found in some subcutaneous organ—perhaps only from the increased warmth—better conditions of nourishment. According to the strength of the poison emanating from them, the skin reacts with the most varied progressive and regressive changes, from the delicate

plasmoma net of the commencing scrophuloderma up to the complete necrosis of the cutaneous fistula.

Local leucocytosis plays here, as in lupus, only an accidental rôle, but it is distinctly greater in scrophuloderma, since chemotactic action is first induced on the leucocytes by the tubercle bacillus when it is dead, and consequently occurs to a much greater degree in scrophuloderma than in lupus.

III.—The Tubercular Ulcer.

We find at the border of the mucous membranes of the mouth, and extending to them, indolent tubercular ulcers, as an early symptom of tuberculosis in inherited cases, usually as the final symptom in general tuberculosis, especially of the lungs, larynx and the throat. These have excavated, irregular, only moderately infiltrated, flabby borders, which develope from the serpiginous extension and the breaking down of miliary nodules. Even on the reddish grey base of the ulcer, we may see these yellow, transparent areas among the weakly granulating surroundings.

This form of tuberculosis, which has chiefly been described by Chiari and Riehl, has a peculiar interest in the whole question of tuberculosis of the skin, although it is the rarest form of it. For here we have the single exceptional appearance of the miliary nodules familiar in the internal organs, whose typical development leads to caseation, breaking down and the formation of ulcers. Were it not clear from the clinical peculiarities of its appearance, it would be seen from the histological study of ordinary cutaneous tuberculosis, lupus, that there must be present here peculiar changes in the the skin, which influence the course of the tuberculosis, so that a less dry, constantly liquefying process developes. But wherein the alteration of the skin is histologically evident, wherein, in other words, consist the fundamental differences of the tubercular ulcer from lupus, is not shown in any of the short publications of the authors, and must remain for future investigation. It is clear that the view, that every yellow spot corresponds to a typical tubercular nodule of internal organs, does not explain it. What must be decided is, what histological factor—be it the necrosis and liquefaction of the cellular new growth or the liquefaction of the interstitial tissue—leads, in contrast to lupus, to ulceration of every individual nodule of the skin. Dr Du Mesnil informs me that the number of tubercle bacilli in the tubercular ulcer is very considerable compared with that in lupus. This would indicate that the bacilli find in these parts of the skin an unusually good medium, but it does not explain the histological difference from lupus.

But because the tubercular ulcer is the one exception in the skin, which approaches the condition in the lungs, it is by no means to be regarded as the type of cutaneous tuberculosis. Only the ordinary form of cutaneous tuberculosis, lupus, can be regarded as characteristic of the effect of the tubercle bacilli on the skin.

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Leprosy.

Leprosy is a universal, chronic, infectious disease, which leads in two different ways to special diseases of the skin. In individuals whose skin is disposed to the growth of the lepra organisms, there develope, from their unlimited multiplication, nodular tumours, the *lepromata*. In other individuals, whose skin does not present a good medium for their growth, the parasites select the peripheral sensory nerves, and by their growth produce, in the skin supplied by the nerves, paræsthesiæ, disturbances of circulation, pigmentary anomalies,

and, finally, nutritive disturbances. The latter (hypertrophies and atrophies) may exist alone or *furnish the basis for a secondary immigration of bacilli.* With or without bacilli, we name them from their origin : *neuroleprides*, and sharply distinguish the papular neurolepride from the leproma, which is often confused with it. Only very exceptionally do the former, after long persistence, pass into the latter. True mixed cases are much rarer than is usually believed. The neurolepride has already been described among the neurotic inflammations.

The *Leproma* is the element characteristic of cutaneous leprosy. It may develope on any part of the skin, but affects preferentially the face, especially the fore-head, eyebrows, cheeks, and regions of the nose and mouth, the ears, then the fore-arms and hands, legs and feet, and in lesser degree the upper extremities, the trunk and the genitals. It almost invariably avoids the hairy scalp, the palms and soles, the axillary and inguinal regions, as well as the smaller flexures, *i.e., the regions where there is greater separation of fat and more profuse development of large coil glands.* Especially characteristic in the diagnosis of cutaneous leprosy from nerve leprosy (the leproma from the neurolepride) is the appearance of circumscribed nodules of the ear, especially the lobule of the ear, the falling out of the outer half of the eyebrows, and the simply regional, not angio-neurogenic symmetry in the lepromata.

The lepromata of the cutis form growths the size of a mustard-seed to that of a plum, they are spherical and of a transparent yellow colour, which may be lighter or darker, tending to brown, from the varying amount of pigment in it. Their consistence is firm—often cartilagenous—so long as they continue to grow, but as they recede they become softer. On section they are very anæmic, have a waxy transparency, are yellowish, smooth, and pretty dry. They are widely distributed, in the milder cases, over the healthy skin, and are isolated. The skin over them is not movable, but united with them. They grow very slowly, may last for decades almost unaltered, and are painless, often anæsthetic. Finally, they undergo either spontaneous or therapeutic atrophy, or they ulcerate, frequently after softening of their contents.

The *lepromata of the hypoderm* form indolent, spherical, firm tumours, somewhat movable under the cutis, which may be easily and completely separated from the fatty tissue. They may develope primarily, but are usually secondary to the lepromata of the cutis or the papular neuroleprides, *for the fatty tissue of neurolepers* is a much better medium for the bacillus than the cutis itself.* Where many of these tumours are present, the skin in nerve leprosy also gets a nodular appearance, and these are the cases which are constantly described by those unacquainted with the disease, as cases of true nodular leprosy. True cutaneous lepromata, on the contrary, develope on the skin of neurolepers, usually at very limited spots, and they are easily distinguished by their appearance, their firmer consistence, lighter colour and sharper contour from the basis of the neurolepride on which they have developed.

The lepromata, taken altogether, give to the countenance a specific physiognomy (Leontiasis), whose almost alarming fierceness is never nearly approached by the flatter, more gradual swellings of the papular neuroleprides of the face, however fully developed. It adds not a little to this striking difference, that the lepromata are frequently margined and separated by straight lines, thicker processes of connective tissue acting as guy ropes to the tumour, while the neuroleprides always affect whole territories of the skin, of rounded form, and therefore never show indentations.

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* I call those persons who suffer from neuroleprides, neurolepers.

The histological formation of the leproma is not so easily studied in its development as that of the neurolepride. For even the small mustard seed nodules show exactly the same form in miniature as the largest pedunculated tumours. Of course the bacillary embolism is the basis of every leproma, as of every neurolepride. But when the original and indemonstrable stage of the emigration of the bacilli from the blood vessels into the tissue is over, the further extension is wonderfully similar. As an example of a fully formed leproma, I select the lobule of the ear, which, in cutaneous leprosy, is usually converted into a solitary nodule of typical structure, because its form will leave no after investigator in doubt, whether we were dealing with a true leproma, for papular neuroleprides of other regions of the skin are very frequently diagnosed as lepromata.

The most characteristic feature of this granuloma lies in the filling of all the lymph spaces of the cutis with organisms, close up to the epithelial structures. Even in unstained sections, they appear, between the perpendicular lanugo hairs, as opaque masses, showing dark against the light sub-epithelial margin, which almost invariably remains free from micro-organisms. With appropriate staining, this peculiar margin is of course more distinct. We then see that the bacilli extend under the surface and parallel to it, at a distance corresponding to that of the superficial blood vessels from the epidermis. These are surrounded on all sides by organisms, which further out are only single or in small groups. In the lymph spaces of the surface epithelium there are hardly ever any, unless other (inflammatory) changes in the epidermis (traumata, suppuration) are added. To a certain depth in the skin this immunity of the sub-epithelial marginal band is respected, along the hair follicles, and always along the ducts of the coil glands. But, beneath the mouth of the sebaceous gland, there takes place in many hairs an immigration of organisms, which almost always in time leads to the mechanical disappearance of the lanugo hair. The epithelial structures are consequently not, as such, immune to the immigration. The connection of the bacilli with those parts of the skin adjacent to the blood vessels, especially at the surface of the skin, rather points to the fact that the normal warmth of the skin is necessary to their existence; the immigration into the hair follicles beneath and into the epidermis in inflammatory processes would be readily explained as exceptions. But besides, the connective tissue must provide a better medium than the epithelium, which is perhaps connected with the presence of fat or fatty acids in the latter. For further observation teaches us (as do clinical facts, see above), that the seats of formation of fat and fatty acid, sebaceous and coil

glands, are completely immune to bacillary immigration. Into the sebaceous glands the bacilli never enter; this I must maintain after years of examination, in spite of opposite views; it must be then that even here other pathological conditions (suppuration) pave the way. In the coil glands we find no bacilli, but very often, in and around them, individual and clustered groups of those globules, already described in connection with the neurolepride, which, like the bacilli, resist acid, and are evidently in some way connected with them. In the ducts and sweat pores, I have not yet been able to discover them.

The fatty tissue itself is an apparent exception to this rule, for it is a favourite seat for the bacillary growth. Nowhere do we find such large, dense collections of bacilli as in the hypoderm. But this exception is only apparent, for where the bacilli are gathered together, the fat cells disappear. The bacilli never penetrate into the fat cells themselves; the fat first disappears, and in the vesicular cavity the bacilli find a soil which stimulates them to luxuriant growth. What takes place is only a very regular substitution of fat cells by bacilli. The muscles are as immune as the glands, only their insertions are often surrounded by swarms of bacilli.

But the nerves have their lymph spaces always filled with bacilli, which surround them up to the sub-epithelial streak. To this is evidently due the local anæsthesia accompanying most lepromata.

The relation of the bacilli to the blood vessels of the skin is of great importance, though not so varied as in the neuroleprides. For the recognition of bacilli in the lumen of the vessels in the lepromata, which is always easy, naturally indicates the possibility of a free circulation of the organisms in the blood. In estimating this we must pay attention to the very apparent source of error, that in the act of cutting, a few of the thousands of bacilli, which are met by the knife, may be transported to other places, and there deposited. A few bacilli at the angle of divided vessels are therefore always suspicious. Beyond suspicion, however, are a few bacilli or collections of them in unopened vessels, and lines of bacillary collections, which evenly clothe the endothelium of divided vessels.

The period of vegetation of the affected bacilli is another point. Here, as in the neuroleprides, we have in the vessels only single bacilli and small, densely-packed, cigar bundle-like groups, lying flat on the endothelium. There is no great production of mucus. If one, therefore, finds a few bacilli which are surrounded by mucus—something like Friedländer's capsule coccus—or vesicular masses with irregularly distributed bacilli, these are not from the lumen of the vessels. Finally the bacilli, as Philippson first pointed out in my laboratory, are not so

easily separated into rows of cocci, which is due to the fact that they have not yet commenced to produce mucus. If one stains with a colour which opposes more resistance to the complete solution of the bacillus into rows of cocci, *e.g.*, fuchsin, we get with appropriate decolorisation the bacillary form in all intra-vascular organisms, the coccothrix form in the extra-vascular.

Even those bacilli, which have penetrated into the wall of the vessel, are mostly naked, and I may mention at once that, even in the true lepromata, we now and again find large stretches of the adjacent cutis, in which only cigar bundle-like, relatively mucus-free collections are present, while all the surrounding parts of the cutis are filled with mucoid bacillary masses. It is very probable that the former are to be regarded as younger, recently penetrated into the cutis, and multiplying.

It is thus beyond dispute, that even in the oldest nodules of cutaneous leprosy, sources of general infection of the body always persist, namely in the flat areas, which cover the intima of many capillaries, arteries and veins of the skin. Their small amount of mucus covering may usually very much diminish the danger of their being washed loose.

Most important and most interesting are the relations of the organisms to the lymphatics and the connective tissue cells; the two are inseparable and must be considered together. Since punctiform areas of fresh invasion of the skin in true cutaneous leprosy were not available, I deduce this relation from the complete lepromata, and from those places in them which show a fresh invasion of the organisms from the blood vessels into the lymphatics, to which the differences just mentioned in the appearance of the bacilli may serve as a guide.

If the leproma is stained for plasma cells, we get at once an idea as to what is protoplasm and what actual cells. We recognise at once that, in contrast to most other granulomata, the mass here is not of a protoplasmic nature (as, for example, in lupus) but that in addition to the deeply-stained epithelial structures, only very few protoplasmic cells exist. In the sub-epithelial marginal streak, which is spared by the new growth, we see the ordinary connective tissue cells of the cutis with very little protoplasm, but in the new growth itself there are only a few cellular areas, which are almost all in the immediate neighbourhood of the blood vessels, and are part of them. They are the endothelial cells of the blood capillaries and the nearest adventitial cells, the latter in most places transformed into a continuous chain of deeply-stained plasma cells. Especially in the angles of division of the blood vessels do we find small collections of five, ten, to twenty such

cells, with relatively faintly-stained nuclei and deeply-stained, often much enlarged protoplasmic mantles. Further away from the blood vessels, large plasma cells only appear singly. But there may be found in their place, scattered here and there, collections of small daughter plasma cells, of the size of lymph corpuscles, but readily distinguished from them by their deep protoplasm stain.

The appearances, got from sections in the three dimensions, show us the vessels of the cutis, of normal structure, with an occasional dense layer of plasma cells, some of which are scattered in lesser quantity through the new growth. All the rest is occupied by non-cellular new formation and naked, large and small nuclei.

Here, as in all the granulomata, the hypertrophic plasma cell is the basis of the new formation; it represents the first and weakest action of the poison. Then comes the question, how does it change; to what structures does it afterwards give place? To answer this we must study those areas of plasma cells, in and around which the younger bacillary colonies, with only a little mucus, are found. We then see that near the large, hypertrophic plasma cells bacilli are almost always absent; they appear first at the side of the smaller plasma cells and daughter cells, which only show a very small ring of protoplasm, and they usually lie at one pole of the cell, as an oval collection of a few bacilli, with a fine clear marginal border. Where larger collections of bacilli cling to a cell, we see very often, from the crossing margin of the two parts, that it is only a dense collection outside, not inside the cell.

If these were the only appearances, protoplasmic cells in contact with collections of bacilli with little mucus, no one would for a moment suppose that the bacilli were in the cells. But something now occurs which has as yet not been observed in other new formations, and therefore has here been usually wrongly explained, so simple is it.

The small ring of protoplasm of the plasma cell completely disappears, and the nucleus clears up, often enlarging considerably. On the other hand, the adjacent collections of bacilli undergo a partial or even total mucoid change, especially the central bacilli being converted into clear, glassy, oval bodies, and only a few, especially the external ones, remaining evident as bacilli. This production of mucus is associated with the necessity of more space, and the spherical masses of bacillary mucus dilate the lymph spaces in which they lie, and compress the one or more connective tissue nuclei lying in the same space, so that they usually become facetted.

These masses of mucus, with or without the accidentally adherent nuclei of atrophic connective tissue cells, have been commonly regarded as unities, cells.

Along with these more frequent changes yet others are found, which lead to very different appearances, at first in the plasma cells. These sometimes show a multiplication of the nuclei without division of the cell, which, since no mitoses are present, I would ascribe to amitotic division, as in the lupus plasma cells. The results are large multi-nuclear plasma cells. If such larger collections of bacilli are adjacent, there is still no tendency to retrograde changes, but, with continued multiplication of the nuclei, they grow round the bacillary collections, as solid, flat, giant cells (chorio-plaques), if small, all round them, if large, they are stuck on one side. These cells, which resemble myelo-plaques rather than tubercular giant cells, and are in general not common, no one regards as, along with the enclasped collections of bacilli, forming a cell.

But even the bacillary clumps do not always swell up to these glassy conglomerations: they retain here and there, though very much multiplied, their original character. There then develope closely pressed, formless collections of bacilli, of the most wonderful sausage and vermicular form and most astonishing dimensions, in which the bacilli cross each other in all directions. Often a few parts in these collections become mucoid, especially the central ones, and there are then formed apparent vacuoles, which, however, have solid, vitreous contents, and are not—as I long thought—hollow. This regular proliferation actually appears also to stimulate the cells of the neighbourhood to proliferation, so that the collections which appear, with bacillary or glœa stain, as deeply stained globi, are usually surrounded by exceptionally large plasma cells or chorio-plaques. The giant globi among them, which, from their size, sometimes represent casts of whole segments of larger lymph vessels or original fat cells, alone escape the suspicion of an intra-cellular position. But even the smaller compact collections of bacilli usually in preparations draw back so ostentatiously from the adjacent cells and giant cells, that they cannot be easily regarded together as cells. These are the easily stained bodies, which were recognised and isolated in the lepromata, in the pre-bacterial period of histology, as yellowish, isolated bodies, "globi" (Danielssen, Virchow, Hansen).

The whole difficulty in comprehending the relationship between the lepra-organisms and the tissue, relates only to *one definite phase of the former*, and is largely due to the ignoring of the production of mucus by the organism, and the accompanying atrophy of the adjacent cells. There was too great a tendency, when one saw a naked nucleus surrounded by bacilli, to regard the contour of the bacillary mucus as that of degenerated protoplasm, and the glœa in general as normal or as peculiarly degenerated protoplasm.

This latter point deserves special explanation, for in it lies the main difference between leprous new formations and other granulomata. The poison of the lepra-organism must be very dilute, for otherwise the millions of organisms in a lepra nodule would not induce such slight pathological changes, almost limited to hypertrophy and atrophy. And it is evidently further diminished in its activity by the mucus of the organism; for the earlier phases of the bacilli and the bacillary collections, which have no glœa, produce almost invariably, when they invade fresh soil, transient appearances of inflammation. It has been stated that the older lepromata often show fatty degeneration. No doubt fresh sections of lepromata, treated with osmic acid and then with pyrogallol, anilin, etc., show many dark brown or black points. Lepromata, hardened in Flemming's solution (better than in osmic acid, for the chromic mordaunt of the collagen assists the selection of the fat by the osmic acid) also show the cutis spotted with brownish red, smoky grey or black points. But any one who is familiar with the glœa of the bacilli will recognise at once that this is not fatty protoplasm but the glœa with the bacilli. We often find *the bacilli as black axial threads* inside oval, yellowish brown collections of mucus. When densely packed, the yellowish, faintly brown masses show a brown, but never a completely homogeneous stain of the whole mass. If then the bacilli are really blackened by osmic acid, it is not to be expected that this reaction would altogether avoid the mucus covering, and it further corresponds entirely with the view here put forward of the different value and different nature of the glœa, that the large masses are made up of smaller ones, which react very differently to the osmium.

So much is certain, that the bacilli, and in a lesser degree the mucus from them, contain in their substance a body which reduces osmic acid. Since this is probably a fatty substance, and since, on account of the assumed fatty degeneration of the protoplasm, the point has not been sufficiently investigated, I endeavoured to stain the glœa with other reagents, and in this I succeeded with *alkannin* and *cyanin* (chinolinblue).*

While the osmium method only does well on fresh preparations, the alkannin and cyanin produce the reaction even in material which

* Since the technique of this method may not be generally known, I give it shortly. *Alkannin:* I fill a small flask with pieces of alkanna root, and fill it up to the neck with diluted spirit. A piece of wool is then pushed in, which acts as a filter, and on it a piece of silk paper so as to preserve the (10-20) sections from the fibres of the wool. The flask is then filled full with diluted spirit, corked and placed upside down over night. The deeply stained sections must be rapidly freed from free fat and precipitates in a 1°/₀ aqueous solution of soap, they are then treated with chlorine water and mounted in levulose. *Cyanin:* The sections are stained slowly over night in a 1°/₀-2°/₀ weak spirituous solution, decolourised in soap solution and embedded in levulose.

has been hardened in alcohol, a sign that the fatty substances are not completely dissolved in alcohol. In good preparations we now get quite a new view of the lepra organism, which only corresponds in one point with the purely bacillary appearances of the leproma after treatment with acid, or the purely coccal form after treatment with iodine. In all these three different forms, the organisms present, topographically, a connected net, which runs through the cutis in narrow meshes, is often swollen into nodules, but even in its finest ramification always shows its connection with other parts of the net.

While the bacillary and coccal pictures show this pretty clearly, our ideas of the nature of the parasites inside the leproma are still further confirmed by the alkannin and cyanin methods. The stained glœa mostly presents itself as spindle or sausage-shaped bundles, of which only individual nodular segments correspond to what are usually described as "lepra cells." It is still more evident here than in fine bacillary and coccal preparations, that these so-called lepra cells are never completely closed structures, but send out processes in a very irregular manner in all directions through the lymph spaces and vessels, to unite with neighbouring ones. Alkannin and cyanin so far resemble osmic acid in their relations to the glœa, that they never stain all parts of it equally deeply. Even with very deep staining, there always remain a few faintly stained or quite unstained spaces or vacuoles, which represent elementary mucus veils, no doubt in connection with the most swollen organisms. A complete *stain of the whole* of the bacillary mucus, which I have not succeeded in effecting, would make the mucus-net still more complete.

From these facts we draw the following very probable conclusions:

The fatty substance, which can be demonstrated, by osmic acid, alkannin and cyanin, in the bacilli and the not too much swollen glœa, is probably identical with that substance, which either produces or contributes to the acid resistance of the bacilli. If acid or alcohol is allowed to act, even for a moment, on deeply-stained glœa specimens, the glœa is immediately decolourised, and the bacilli appear in it deeply stained, indicating that the enclosed bacilli are also stained.

Then the distribution of the bacilli, in the form of an almost complete net, makes it very probable that the organisms possess no independent movement. Movement is caused by the lymph-stream, the growth, and the movements of the skin, and the advance is so slight that the space which developes is immediately bridged by the mucus.

Further, it is clear that inside their mucus-net the organisms must lead an inert existence, and be relatively innocuous. The arguments of Hansen and others, that the innocence of the bacilli is due to their

encapsulation in animal cells, are equally available, and more rightly so, for their encapsulation in vegetable mucus. Is there then a true fatty degeneration of the cells, which can induce appearances other than that of fatty glœa, which recall ordinary, breaking down, fatty granular cells ?

I have never succeeded, even in the oldest, non-suppurated lepromata, in finding traces of fat in the cells of the connective tissue. On the contrary, the fat disappears everywhere under the influence of the stagnatory œdema and the pressure atrophy, even from the fat cells of the hypoderm. In the cells embedded in the mucus, we could not of course expect any fatty degeneration, for their protoplasm is completely atrophied. It can only take place in the endothelial giant cells, in which a fatty degeneration of the protoplasm, somewhat analogous to the secondary degenerations of the lupus giant cell, might occur. But that would be evident in preparations hardened in Flemming's solution, and in spite of careful investigation I have never observed it. Even if present, it is not a regular appearance in the lepromata.

Nor is there a pigmentary degeneration of the connective tissue cells, even in the skin of coloured races. There are appearances which, at the first glance, look as if large sub-epithelial cells contained, in their protoplasm, bacilli and masses of pigment. But a good plasma cell stain shows at once the simple juxtaposition of bacilli-containing glœa and pigment-containing protoplasm in the same lymph spaces. And often enough we can further recognise, that much of the granular pigment is not seated in the cells under consideration, but lies free, and only comes into contact with the endothelial cells because it occupies the same lymphatic. Formation of pigment and movement of pigment have nothing in common with the bacillary growth. The dropsical swelling assumed by many authors depends on confusion of the glœa with "degenerated" protoplasm.

We can then only determine the following changes of the connective tissue cells in the lepromata :

1. A *hypertrophy of the connective tissue cells,* which leads to the formation of large, spherical, protoplasmic plasma cells. These are formed mainly along the vessels, to a lesser degree between them. The large plasma cells either divide completely, leading to groups of small daughter cells, which, though often of the size of leucocytes, are easily distinguished from them.

2. Or the plasma cells, by the breaking down of the nucleus, contain several nuclei, without themselves dividing, and may grow from this still spherical stage—especially in contact with actively growing bacilli—into *large multi-nuclear masses of protoplasm* (*chorioplaques*).

3. Their most frequent transformation is, however, the same as that of all the connective tissue cells in contact with the lepra bacilli. *Their protoplasm gradually completely disappears, while the nuclei become paler, but otherwise* — like the nucleoli — *remain preserved.* Indeed, the achromatic substance, which at the stage of plasma cells was small compared to the chromatic, in many cases evidently increases, and thus we rarely find such large, naked, connective tissue nuclei as in the lepromata. As the organisms continue to grow, and the tension of the tumour becomes greater, the nuclei become facetted. An intimate connection between the lepra-organism and the connective tissue cells is therefore not to be denied. On the contrary, the bacilli evidently consume the protoplasmic part of the cell and the chromatin of the nuclei, without affecting its achromatic part. But they do not penetrate into the plasma cells, still less into the normal, meagre connective tissue cells, which, even apart from their want of motion, would be very difficult on account of their rapid growth. We may rather say that the organisms grow round the cells, if we bear in mind that the complete involvement of the nucleus is only the result of the disappearance of protoplasm on the one hand, and on the other of the great swelling of the organisms, and the consequent spindle or spherical dilatation of the lymph spaces. When the bacilli are single or arranged in the cigar bundles or in large globi, there can be no question of an enclosure but only of an application; juxtaposition. But in all stages, even as completely swollen, vitreous collections, with a few bacilli and atrophic nuclei, the whole mass of the organisms simply lies in the lymph spaces of the skin, as was noted by Vandyke Carter * of his micrococci and their zooglœa, even in the pre-bacterial period.

We must therefore, in a few words, more closely consider the implication of the lymphatics. Since the actual lymphatic vessels inside the skin always commence and run as far as possible from the blood vessels, so that a lymph vessel lies in between two blood vessels and *vice versa*, the organisms escaping from the blood stream do not directly reach the lymph vessels, but first pass into the lymph spaces, that is, they occupy the space which is usually occupied by the tissue juice, which normally remains free between the collagenous elastic tissue and the connective tissue cells. Since they almost continuously dilate these spaces in spindle form, as is shown by the alkannin preparations, the limitation of space and the tissue pressure in the cutis proper become maximal, and it is of course those larger lymph spaces, which are always found in yielding condition;

* Path. Trans., Vol. XXVII.

the endothelium-clad lymph vessels proper, which suffer most, are most compressed.

It depends simply on the rapidity of the advance of the organisms whether they reach the lymph vessels proper, inside the cutis. If they do this, before the surrounding tissue pressure becomes too great and reduces them to the calibre of ordinary spaces, they find here at once, as in the cavities of atrophic fat cells, in the seminal canals and other pre-formed spaces, a good site for luxuriant proliferation, and thus develope the colossal, vermiform, hour-glass, even spirally twisted globi, which have been noted by every investigator, and as to whose inter-cellular nature there has been no serious doubt. These masses are, however, only occasionally part of the net of mucoid bacilli, which mainly occupies the lymph spaces, not the lymph vessels.

A further, natural result of this general infarction of the lymph spaces in the cutis proper, is the tendency of all leprous skin to stagnation of lymph in the parts free from infarcation. This is seen in the non-leprous sub-epithelial zone, whose lymph spaces and vessels are distended into large reservoirs of lymph, as Hoggan * long ago demonstrated by means of the silver method. The larger lymph vessels and spaces in the neighbourhood of the nodule are also wider than normal. But this local stagnation of lymph around the individual nodules does not lead to such marked appearances of stagnation as very soon accompany the flat neuro-leprides of the extremities. Even the results of this hypertrophy of the collagenous tissue and the epithelium; scaling, ulceration, etc., appear more rarely and later here than there. But the local stagnation of blood is very pronounced in and around the nodules, for the same reason as in the neuro-leprides. There only the vessel sheaths, here the whole cutis is converted into a stiff, inelastic tissue, and this explains the slower flow of the blood, and the dark bluish colour of all dependent and less infiltrated nodules. This is, especially on the upper parts of the trunk, the upper arms and the face, only overcome by the pressure anæmia in the very tense nodules, and thus the transparent yellowish colour of the organisms is here mainly evident. There is also, in all older lepromata, an obliterative inflammation of certain vessels, arteries as well as veins, which, though it may help to slow the blood, can never be regarded as the cause of the invariable stagnation.

The collagenous tissue around the leprous nodules is pressed asunder and split up by the dilatation of all its spaces. The individual fibrillary bundles then disappear, partly with the formation of plasma cells, partly, and in an ever increasing degree, from the pressure of the

* G. Hoggan on the condition of the lymphatics in Eastern leprosy. Trans. Path. Soc., Vol. XXX.

growing colonies of bacilli. In the densest and firmest nodules, the collagenous frame-work forms only a relatively delicate net of rounded meshes, in which the original bands of fibrillary bundles, crossing each other at acute angles, can no longer be recognised. After certain traumata, (*e.g.*, discision of the nodules), more rarely spontaneously (Leloir), a fibromatous process attacks the leproma, a connective tissue, parallel to the surface, arranged in regular layers, mixed with flat protoplasmic cells, appearing in place of the destroyed and absorbed granuloma tissue. But this is rare.

More frequently, the bacillary masses in old nodules are simply absorbed, without new masses of connective tissue being formed, and there remains only the sack-like, more or less pedunculated growth, whose areolar connective tissue resembles that of a molluscum (fibrosum).

The elastic fibres disappear at once when the leprous new growth is established; they terminate abruptly around the nodule. But we often see fine remains and fragments of them at the periphery of the nodule, though I have never found them, as so frequently in lupus, enclosed in giant cells. In the rare fibromatous new formations which replace the leproma, no new elastic fibres are formed.

In the old cutaneous lepromata, especially when a spontaneous or therapeutic absorption has been induced, and therefore many lymphatics opened, suppuration occasionally occurs from accidental infection. The lepromata themselves never suppurate. Ulceration is therefore most likely to occur on the elbows, knees, ankles, backs of the hands, and face, which are most exposed to injury. The ulcerations have therefore no special anatomical interest, very simple means suffice for healing, and even the oldest lepromata are very rapidly skinned over.

We may therefore define the leproma of the skin as a diffuse granuloma, whose peculiarity consists, on the one hand, in its limitation to the connective tissue elements, and especially to the lymphatic system of the skin, and on the other in the enormous growth of organisms, whose number far exceeds anything we are accustomed to find in other infectious diseases. As opposed to these constituents, the plasma cells, the actual granulomatous growth, are very unimportant in number and significance; the main interest therefore hinges, not so much on the fate and *further changes* of these cells, as *on the organisms themselves*, especially the *production of mucus*, which causes the increase in size. To the paucity of the cellular elements and the preponderance of the organisms dormant in the bacillary mucus, the remarkable indolence and relative benignancy of these growths may be ascribed.

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Leukæmia.

In addition to general anæmia and a tendency to hæmorrhage in the last cachectic stages, multiple tumours have been noted on the skin in leukæmia. Bisiadecki first observed, in a man fifty years of age, with marked leukæmia, pale, lentil-sized, somewhat elevated, smooth, soft nodules, movable with the skin, sometimes depressed in the centre, sometimes scaling. They were close together on the face and back, but scattered on the neck, breast, and extremities. Similar nodules were observed, by Hochsinger and Schiff, in a leukæmic boy eight months old: flat, firm nodules, the size of a pin head to a hazel nut, yellowish red to brownish red, movable with the cutis, distributed all over the body, particularly on the hairy scalp, face, and forehead, with a smooth, now and again dimpled or scaling surface. The lymph glands in the neck and groins were greatly swollen.

In these cases the authors found nodular, cellular infiltrations in the skin, especially at the border between the cutis and hypoderm, by which the upper fat lobules were transformed into lymphomatous structures, and the coil glands closely sheathed. The infiltration extended from the capillaries of the coils and the upper fatty tissue, in a lesser degree from the perifollicular capillaries, and consisted throughout of lymphoid cells, without any spindle and giant cells. The papillary body and the upper part of the cutis were almost free from infiltration, with the exception of the central part, where the infiltration, corresponding to the external dimple, met the epidermis. There were no blood vessels in the nodule; the peripheral ones were dilated and distended. The coils inside the nodules were well preserved.

The cases of Oliver and Philippert also come under this category. In Oliver's case, after a bruise of a metacarpal bone, nodules appeared in the fossa supraclavicularis, and then in the axilla. General swelling of the lymph glands, liver and spleen immediately followed, with an eruption of numerous (sixty) hard tumours of the hypoderm, varying in size from a bean to an egg. The leucocytes in the blood were very much increased. The subcutaneous nodules showed the structure of round celled sarcoma. In Philippert's case the first nodule appeared on the temple, four years before death, and was followed by subcutaneous tumours on the head and face, from the size of a pea to that of an egg, covered by normal but brown stained, smooth skin and ectatic veins. Nodules appeared on the mucous membrane of the nose and throat. Death occurred, with general swelling of the glands and other leukæmic symptoms. The cutaneous nodules had an adenoid structure.

Common to all these cases is the nodular limitation of the new formations, their rapid, multiple appearance, usually after a primary tumour of the skin or the lymph glands has existed for some time, their development from below upwards, and their frequent limitation to the hypoderm, finally, their slight tendency to repressive metamor-

phosis and ulceration. Histological examination has not done much to make clear the actual character of these growths; from a few scattered indications on the nature of the cells, they appear to have been a special form of granuloma, developing in the neighbourhood of the coil glands. This, at all events at present, appears the most probable view, and is by no means contradicted by the discovery of a "sarcomatous" structure, nor by the ever recurring report of a "lymphadenoid" structure, even if this is not influenced by the presence of the general leukæmia. For we know that all granulomata of the skin, consisting of plasma cells, show a rarefied, and, when brushed out, an "adenoid," collagenous frame-work. A thorough investigation of the cells with modern methods is required to determine their nature.

In addition to this nodular form of leukæmia of the skin, Neuberger has recently described an apparently different form, which appears in the form of a few solitary, brown nodules, projecting over the level of the skin, which are lobulated and firm, grow slowly, and may last for years, and rather recall the dermatoses in pseudo-leukæmia.

Neuberger found a dense infiltration of the cutis, consisting of small lymphoid cells, especially around the dilated, comedo-containing follicles, by which the ridge net of the much diminished epidermis was flattened out and separated from the infiltration of the cutis by a small, uninfiltrated zone of connective tissue. Further, the surroundings of the coils, the hypoderm, and the muscles (skin of the cheek) were infiltrated with "granulation cells"; the coils themselves were intact. In their surroundings, where the author recognises the origin of the growth, the "lymphoma growth" is better marked, through the sharp margining of the cell masses, than in the upper parts of the cutis.

We shall not go far wrong if we regard this very obstinate form of leukæmic cutaneous nodule also as a granuloma, and not as a collection of leucocytes—a lymphoma. The well marked cellular areas, appearing in the depths of the cutis, correspond to the general appearance in most infectious growths, and the clinical relations correspond exactly with a tuberous spot, present in a case of pseudo-leukæmia, which I found to be a typical granuloma.

Further, the cases of Hochsinger and Schiff show that there are transitions between the pale red, soft, entirely subcutaneous, multiple tumours and the yellow to brown, firmer, superficial, elevated ones and solitary tumours. Probably, as in syphilis, external influences, concomitant dermatoses, &c., determine the different localisation and the type of the nodules. This is especially the case in a third form of

the leukæmic dermatosis, a *diffuse* form, which has been several times described. The most familiar case is that of Kaposi.

> Accompanied by a partly diffuse, partly areated scaling, and moist eczema, especially of the head and hands, less of the upper extremities and upper part of the trunk, there appeared, on the one hand, diffuse, doughy swellings of the skin and the subcutaneous tissue, on the other, tumours, from the size of a pea to that of a pigeon's egg, which ulcerated spontaneously, and left behind them large, flat, red losses of substance. The face was swollen by œdema and nodules, and almost leonine. With swelling of the glands and spleen, leukæmia, and general cachexia, death ensued after several months.

Sections through the skin showed the hypoderm very œdematous, brawny, grey, sharply margined from the healthy, yellow fatty tissue, the interstitial tissue between the fat lobules, thickened and condensed, running through the brawny masses in the form of white septa. These brawny masses, 1-1½ centimetres thick, showed a nodular or warty form and a lobulated construction, and were not sharply defined from the healthy surroundings. The cutis over the nodules was either œdematous, deeply reddened and ulcerated, or united with the nodules, and fatty. Microscopically, all the tumours consisted of an avascular, delicate stroma, packed with leucocytes, especially around the coil glands. The hair follicles were unchanged, the sebaceous glands and coils surrounded by cellular infiltration, and the cellular elements of their walls (?) swollen, the prickle layer partly proliferated, partly rarefied from the pressure of the growth.

Galliard described a similar case, some years ago, which showed especially the diffuse leonine thickening of the skin of the face.

> It began with a nodule on the breast and swelling of the axillary glands. Death took place nine weeks after, with marked leukæmia.

In addition to lymphomata of the liver, testicle, pancreas, and kidneys, enlargement of the lymph glands, liver, and spleen, there were found cutaneous nodules of "reticular formation," especially around the sweat and sebaceous glands, and between the fat lobules, while in the recent nodules the upper layers of the skin were almost unchanged.

> In this case, as in those of Leber and Chavel, the eyelids especially were the seat of diffuse infiltration. Subcutaneous swellings and nodules could be felt under the bluish brown, thickened, tense skin, which was covered with ectatic veins. Both cases of leukæmia ended fatally.

The microscopical observations in this case also refer to round cells in a fibrous reticulum, and revision, with better and more modern methods, is urgently required.

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Pseudo-leukæmia.

This general disease (Lymphadenoma, Hodgkin's disease), resembling Leukæmia, but without changes in the blood, also leads to affections of the skin. The commonest is a form of granuloma, closely resembling lupus and the tuberous syphilides, which we are more familiar with, histologically, than with the leukæmic growths. J. N. Hutchinson first described a case of Hodgkin's disease, in which 139 nodules, the size of peas to walnuts, appeared in the cutis and hypoderm, after a swelling of the cervical lymph glands had introduced a general lymphadenoma. The *post mortem* further showed nodules in the lungs, vertebral bodies, the peritoneum and the cortex cerebri. The cutaneous nodules had an adenoid structure. Recently Arning more thoroughly described a case, in which firm, flat, elevated, painless, yellowish brown, transparent, waxy nodules appeared at the point of the nose, the alæ nasi, the nasal septum, the upper eyelid, and under lip, then on the gums and the uvula; they were, here and there, covered with ectatic vessels, surrounded by hyperæmic halos and were not ulcerated. There were also found indolent, subcutaneous, and intra-muscular firm tumours of different sizes, on the face, neck, and arms.

The examination of a cutaneous nodule showed that the whole thickness of the cutis was permeated by a mass of granulation, whose origin Arning ascribed to the capillaries of the coils, and which reached into the papillary body or even into the prickle layer, so that the growth itself threatened to burst the epidermis. There were no giant cells, no necrosis, and, in spite of the long duration, no sclerosing of the connective tissue; there was, however, thickening of the vessel walls. Bacteria could not be recognised.

I observed an exactly similar case in a young girl, who suffered for a long time from severe anæmia and a very large splenic tumour, without any evident leukæmic symptoms in the blood. There appeared, first on the left upper eyelid, then pretty rapidly on the forehead, the nose and the chin, in the naso-labial furrow, on the hairy scalp, the neck, and scattered on the arms and legs, lentil-sized, transparent, shining, flatly elevated, firm papules, of a brownish

yellow, or, as the anæmia increased, greenish yellow colour and smooth surface. Some showed a slight dimpled depression in the centre, others a fine papery scaling. They closely resembled, except for the difference in colour, the large papular syphilide, but did not react either to mercury or to iodide. The submaxillary glands and a few glands in the neck swelled up into firm nodules. The tumours of the glands and the eruption healed and the general condition improved much under arsenic. There were no subcutaneous nodules, as in Arning's case.

A spot excised from the back showed, even histologically, a great resemblance to a syphilitic papule. The greater part of the pseudo-leukæmic papule consists of a dense plasmoma of the papillary body, which, as in the syphilide, has developed from the coalescence of cellularly infiltrated, vascular cords, and only in the centre extended, through the centre of the cutis, to the deep vascular net. Here also the lymphatics are dilated, and free from plasmomatic infiltration. There is, however, this characteristic distinction from the syphilitic plasmoma, that the endothelium of the vascular capillaries and the immediately adjacent perithelium do not take part in the swelling, so that the pseudo-leukæmic plasmoma first appears sharply marked at a distance of one or two cells outside the vessels. The cellular infiltration of the papillæ is especially great, but consists mainly, simply of swollen and rounded connective tissue cells, only a few plasma cells and a moderate number of leucocytes. They are swollen like clubs, and the epithelial ridges between them are consequently thinned. In the centre of the papule, indeed, the papillæ run together into a uniform cushion, completely obliterating the epithelial ridges, and stretching and thinning the prickle layer above. This configuration of the papillary body is a result of the complete absence of mitotic proliferation in the epithelium, and this is a second noteworthy difference from the syphilide. The external smoothness and the shimmer of the pseudo-leukæmic papule depends on the stretching of the passively-thinned epithelium, over the whole papule. Further, not only do leucocytes penetrate into the dilated lymph spaces of the epithelium, and form, here and there, tiny, dry abscesses in the prickle layer, but even parts of the cellularly infiltrated papillæ push themselves into the prickle layer; the withdrawal of the epithelial ridges from the swollen papillary body does not take place all at once, but by irregular advances of the border.

The third important difference between the leukæmic and the syphilitic papule consists in the complete absence of regressive changes of the plasma cells; we find none homogenised, and no giant cells. The plasmoma persists—at least judging by the excised papule—for a long time in the stage of simple granulomatous growth. This circumstance may have led many of the earlier investigators, who worked

only with nuclear stains, to declare pseudo-leukæmic and leukæmic tumours to be lymphomata; giant cells and degenerations were not present, and the plasma cells escaped them; so their conclusion of the presence of leucocytes alone was natural enough. In this papular exanthem, which I have described, leucocytes play a very unimportant rôle. They are found always only at the epithelial margin and in the epithelium, which they help to loosen.

The other symptoms are of no great significance. Over the thinned prickle layer, the granular layer has disappeared, the horny layer is nucleated, *i.e.*, the epithelium has undergone ordinary parakeratosis and is thrown off in scales. Between the horny layers are found spaces, filled with leucocytic nuclei. Mast cells are only very sparingly present, but there are a good many pigment cells in the papillary body.

If we review all this, we have before us a characteristic, papular, pseudo-leukæmic granuloma, which is constructed like the syphilitic papule, and is distinguished from this by the absence of regressive cell forms and epithelial proliferation, and by the fact that the perithelium does not share in the growth.

Joseph recently described, in a case of lympho-sarcoma of the cervical and mediastinal glands, arising from a tumour on the lower jaw, deep cutaneous nodules, the size of peas to walnuts, on the neck and trunk.

Histological investigation showed: the epidermis and upper layers of the cutis normal, and the seat of the nodes in the lower layers of the cutis and in the hypoderm around the coils. These were not sharply margined, and consisted of cords and nets of regular, round and spindle formed cells, with vesicular nuclei and little protoplasm. The cells sometimes lined cavities, as if they had developed from the endothelium of the blood and lymph vessels. The coils were separated by layers of connective tissue from the masses of growth.

If Joseph made the diagnosis of lympho-sarcoma of the skin from these histological appearances—and not rather from the sectio and the clinical appearances—he has not supplied proof of it, so that the case is of no value to our knowledge either of pseudo-leukæmia or sarcoma of the skin. It differs from Arning's and my cases in every particular. Joseph had already attributed a dermatosis, with itching papules like prurigo, to pseudo-leukæmia. The histology of this papule also is still awanting, so that neither of Joseph's lympho-sarcomatous nor of his pruriginous form of pseudo-leukæmia can we give such a definite description as of the papular, pseudo-leukæmic granuloma.

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II.—Acute Exanthemata.

The *acute exanthemata* form a good example of what was said above in relation to the classification of inflammations of the skin in general, namely, that similar causes, acting on the same organs, may induce the most different pathological results. Thus the members of this natural clinical group appear, when superficially considered, to require, anatomically, very wide separation from each other. At most one would be inclined *a priori* to leave together measles and scarlet fever on one hand, chicken-pox and small-pox on the other, placing the former with the serous inflammations of the skin, the latter with the inflammations of the epidermis.

But more thorough histological investigation of these diseases suggests a better arrangement. It is at once evident that the ordinary symptom of acute inflammation, especially the emigration of white blood corpuscles, plays in measles and scarlet fever generally a very limited rôle (often none at all), that in varicella it only shares to a very slight degree in the processes, and in small-pox only *after the development of all the main appearances*, and though it is then well marked, is still a factor of slight pathological significance.

We find further that the peeling which constantly accompanies measles and scarlet fever, and clearly enough distinguishes them from simple disturbances of the circulation of the skin, cannot be regarded, like other scaling (*e.g.*, in the dry catarrhs), as the simple result of an exudation in or between the epidermic cells, for the prickle layer appears hardly altered, and the amount and duration of the process of scaling is in no direct relation to the free serous transudation in the cutis. If we have to regard this striking epidermic change as a characteristic primary result of the cutaneous poisoning, then it does not appear any longer so utterly different from those epidermic changes of small-pox, which lead to necrosis, but only as a slighter degree of them. And this view is only confirmed by the rare, though occasional occurrence of severe vesicular changes of the epidermis in measles and scarlet fever.

If the apparently incompatible appearances of the different exanthemata may nevertheless be arranged in a uniform series in relation to the epidermic changes, if we have to do in all cases with a direct poisoning of the epithelium, and only with different degrees

of it, we recognise also in the changes of the cutis, different as they are, a uniform scheme. Measles and scarlet fever show us excessive disturbances of circulation, the one of the type of stagnatory, the other of paralytic hyperæmia; for neither, can we find mechanical, but only chemical, toxic causes. The œdema of measles, with its stagnatory hyperæmia, is no more a typical inflammation than the hyperæmia of scarlet fever with no œdema. But there is found in both, a slight hyper-nutrition, a multiplication and enlargement of the connective tissue cells, which we may regard as a slight degree of parenchymatous inflammation. In varicella this is more marked, and in small-pox at the first stage it may be so great as to lead to the development of plasma cells around all the vessels. But here the toxic action of the poison on the peripheral circulation is much reduced, as is its wide influence on the whole epidermis, and therefore the phenomena of scaling are limited to the seat of the localisation of the poison in the epidermis.

If, in this sense, we review these dermatoses, it must be admitted that, in view of the multiformity of the appearances, all the simple familiar schemes of inflammation are insufficient. What is common to all processes is, first, a direct and primary localisation of the action of the poison in the blood vessels of the skin, to which these respond, either with greater disturbance of the vasomotor apparatus, or by a progressive disturbance of nutrition of their immediate surroundings. Then we have, again, a more or less energetic *primary action of the poison on the epidermic structures*, which is indicated by general and weaker, or localised and more serious disturbances of nutrition.

In addition to this extension from the vessel walls to the epidermis, the acuteness of the primary action is common to all processes; in this they show a certain analogy to those dermatites caused by external traumata. In all, the action of the poison is soon exhausted, the infectious agents find their grave in the skin, after they have induced their action. We can therefore distinguish a period of invasion and one of reparation, analogous to the traumatic dermatites. The greater the attack on the structure of the skin, the more complicated and prolonged is the latter, particularly in small-pox.

In this very point there is a great want of accord among the acute exanthemata, but, if one has recognised the value of this common basis, even in anatomical relations, it really matters little whether we give to the lowest degrees of this poisonous action the name of inflammation; for in the highest (small-pox), there can be no doubt of it. To decide this question, we have to apply to practice, which had established the definition of inflammation, especially for the skin, long

before there was any question of histological examination. And practice rightly determines, in all the acute exanthemata, the existence of acute inflammation; for all the cardinal symptoms: Tumor, Calor, Rubor, Dolor, Functio læsa, are present. We consequently learn, that even acute inflammations of the skin may exist, without showing the histological characters, of emigration of leucocytes, parenchymatous clouding of the protoplasm, interstitial exudation and vascular dilatation; the exudation is absent, *e.g.*, in scarlet fever, and the vascular dilatation in the skin of fatal cases of measles.

The single, everywhere recognisable, though often very feebly developed symptom of inflammation, consists in the swelling and multiplication of the perithelium of the blood vessels. Slight as this is, it is important, as often the only indication of an inflammatory disturbance of nutrition, a "parenchymatous exudation" of the cutis, persisting after death.

On this common basis *of an acute inflammation, extending from the vessels of the skin more or less widely into the epidermis*, are formed the individual acute exanthemata, by the addition of different, and for each disease very characteristic, toxic actions, which select sometimes the vessels and nerves, sometimes the epidermic cells. It is these which dominate the post-mortem histological appearances, and therefore induce the apparent want of agreement in the observations.

To the four main diseases of this group I add two rarer ones, a pock-like eruption from a septic infection with streptococci, and a pustular one, from an infection with staphylococci. These permit of the definite recognition of the infectious agents as the cause of the cutaneous eruptions, and may therefore serve to explain the spread of the infection in the exanthemata. In spite of their rarity, I will describe them very particularly, especially the streptogenic phlyctenosis, which is a true example of the pock process.

Measles.

The eruption of measles is characterised clinically by isolated roseolæ, of the size of peas to lentils, roundish, frequently somewhat irregular, but always sharply defined, of a yellowish-red to bluish-red colour, and showing slight papular swelling. The latter either affects the whole spot, which is then swollen, or more frequently only the central zone, which is then somewhat elevated over the rest of the spot. The roseolæ soon pale, and then scale more or less severely, but the scaling is always branny, corresponding to the isolated spots. They often leave slight pigmentation. Rarely, at the height of the eruption, there may be a few vesicles developed; more frequently there are small hæmorrhages in the papules.

These clinical symptoms point to the fact that spastic resistance in the cutaneous vessels is added to the primary, congestive hyperæmia

which developes around the infection in the capillaries, and this explains the cyanotic colour, the papular swelling and the urticarial œdema of the centre, as well as the frequent escape of the colouring matter of the blood. It is therefore not remarkable that spots of measles excised from the dead no longer show any hyperæmia, and that the blood vessels are not, as in scarlet fever, dilated. But there are two distinct signs of the previous presence of œdema. The rapidly developing and spastic œdema always collects at the place of least resistance, and as we are mostly dealing with young children, that is in the fatty tissue around the coil glands, and in the sheaths of the larger vessels, the cutaneous muscles and the follicles. We therefore find the fat lobules very œdematous, resembling, in alcohol preparations, large spaces in the tissue, only occasionally containing much dilated areolæ and rarefied connective tissue septa, and, in a corner of the upper end, the coil gland compressed by the œdema. The individual coils, the hair follicles and the muscles seem to swim free in widely dilated spaces. Further, we note, in the lower and central parts of the cutis, circular, oval or irregular spaces and passages, which are to be regarded partly as dilated lymph vessels, partly as enormously dilated lymph spaces. Only occasionally, especially around the hair follicle, may these dilated lymph spaces be seen to reach the papillary body. We only get a proper demonstration of this œdematous condition of the cutis, which so thoroughly explains the clinical appearance of the measles papule at the height of its development, in thick sections, which allow us to follow the course of the spaces, especially if the elastic tissue is well stained, for this is pushed aside by the swollen lymph spaces, and retains its altered position even after excision.

In addition to the positive observation of œdema of the cutis and the hypoderm, the almost complete absence of a cellular exudation is of equal importance. The migration of white corpuscles is not more than in all simple stagnatory hyperæmias, less indeed than in most. Therefore there are few leucocytes in the epithelium. The prickle layer is not widened, as the œdema does not extend to its lymph spaces. I have not found mitoses at the acme of the process; they only accompany the scaling. But there are already appearances of anomalies of cornification, the granular layer partly disappearing, while the basal horny layer is thickened. At the stage of scaling, the super-basal horny layer separates itself from the basal, and, with the central and upper horny layers, forms the scale. Mitotic proliferation replaces the lost epithelium.

This description relates only to the ordinary flat or slightly papular eruption, which alone was procurable. Catrin has recently

examined a case of "rougéole boutonneuse," and found many differences. Possibly Neumann examined similar preparations, for both authors agree in describing, in the papule, marked diapedesis of white corpuscles (Catrin), "round cell growth" (Neumann), especially along the blood vessels, follicles and coil glands. But Catrin further described, as characteristic of the nodular form of measles, a series of deep epithelial changes. These commence with the colloid transformation of a few, deep-lying epithelial cells, in their perinuclear zone. The colloid endoplasmata form very refractile masses, staining deep red with eosin and picro-carmin, and surrounding the nucleus in semi-lunar or ring shapes, which, after the ectoplasm of the epithelial cells has considerably increased, rupture and run together. These colloid areas are distinct at the periphery of the papule, in the centre they are often present in masses. Around them the lymph spaces of the epithelium gape, and there appear fissures in the prickle layer, which are filled with coagulated fibrin and leucocytes. In the centre of the papule there appears, from confluence of the colloid masses, a zone of coagulative necrosis inside the prickle layer, which consists of acidophilic epithelia, whose nuclear chromatin is partly gone and converted into round balls with or without colloid masses, of free colloid masses, leucocytes and red corpuscles, and which is densely permeated by thready fibrin. Although the lymph spaces of the epithelium in the neighbourhood are dilated, the spaces of the prickle layer are not filled with fluid lymph, but with small coagula, and lead only to a moderate elevation of the horny layer. Since the colloid degeneration, to which the necrosis and the formation of spaces succeeds, mostly affects the basal prickle layer, the main fissures are usually sub-epithelial, between the swollen papillary body and the surface epithelium. The name "deep phlyctenula," which Catrin gives it, is not used by that author in its strictest sense, for we are not dealing with an ordinary vesicle (with more fluid than solid contents). From Catrin's descriptions and drawings, the epithelial degeneration and necrosis do not appear to me to be the necessary causes of the deep phlyctenula, for the latter, *i.e.* the circumscribed elevation of the whole epidermis from the papillary body, is a phenomenon which appears in almost all acute swellings of the papillary body, with loosening of the epithelial cutis margin. But the spaces, filled with fibrin, in the neighbourhood of the colloid epithelium, are no doubt the results of their degeneration and swelling. It appears to me important, that Catrin only observed emigration of leucocytes from the papillary body at those places where the surface epithelium contained colloid cells, and that on the other hand the centre of the papule, where the epidermis was most degenerated, never showed such

distinct emigration as the periphery of the papule. Catrin ascribes this striking condition to the opposing pressure of the phlyctenula, which is greatest at its centre; but such mechanical pressure from without never prevents leucocytosis (*conf.* Small-pox, Impetigo). It rather appears to me to be the result of the fact that the inflammation, with the local leucocytosis, follows on a stagnatory hyperæmia, and developes on a soil altered by spastic œdema. The same increased pressure, which the spastically closed lymph spaces exert on the whole contents of the cutis, and which on excised spots of measles overcomes every vascular dilatation, must, in the centre of the measles papule, make emigration most difficult. This secondary inflammation, unknown in ordinary measles, but characteristic of the "nodular" eruption, consequently forms, according to Catrin's very plausible views, a peripheral zone around a more œdematous (spastic œdematous) centre.

The colloid change and necrosis of the epithelium in these severe cases are certainly more than a higher degree of the simple œdema of the epithelium in the ordinary papule of measles. We must rather regard them as a direct result of the poison, which has somehow, exceptionally, reached the epithelium, as it does in small-pox. The subepidermoidal phlyctenular formation, on the contrary, may be explained, purely mechanically, from the rapidly developing separation between epithelium and swollen papillary body. The scaling of the epidermis in these severe cases is naturally more profound and persistent.

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Scarlet Fever.

The eruption of scarlet fever has the form of dark red points, of the size of turnip to mustard seeds, which are surrounded by lighter halos. These run together, on most parts of the body, to a diffuse, scarlet, punctate redness. The skin at the same time becomes somewhat œdematous, without the centres of the spots projecting over the surface, as in measles. The redness completely disappears on pressure, but at the height of the eruption a yellowish colour still remains. In a few cases (particularly in certain epidemics) papules are formed, which pass into small, distinct vesicles, so-called "purples." Immediately after the disappearance of the eruption, or a few days later, the horny layer commences to peel, in large, coherent lamellæ. In severe scarlet fever there often appear hæmorrhages, in the form of small petechiæ, more rarely of larger suffusions.

The first striking symptom, which sections through acute scarlet fever skin always show (in all the seven cases which I have examined), is a marked wrinkling of the whole epidermis, along with the papillary body, in contrast to the cutis, which is tense and relatively shortened, beneath. This contrast of the surface to the rest of the skin is most evident when the elastic tissue is well stained. The usual gradual transition of the elastic net of the cutis into the finer one of the papillary body has disappeared; the former is closely arranged, as nearly as possible parallel to the surface, up to the margin of the compressed papillary body; evidently the coarser fibres of the latter are withdrawn, for only a few, very fine ones, reach perpendicularly into it.

This appearance, which is seen in many different dermatoses, is always to be ascribed to a want of relation in space between the epidermis and the cutis, and is here evidently induced by an over-stretching of the epidermis by the sodden, engorged cutis. After excision, the latter contracts vigorously, the over-stretched epidermis cannot follow it, and the papillary body is thus thrown into folds. This symptom points to the fact that the cutis in life was not, in the ordinary sense, œdematous, for then it would have lost its elasticity. And further, we miss in scarlet fever those œdematous spaces and that œdematous fatty tissue which we find in the cutis of the papules, at the height of measles.

The cutis of the scarlet fever skin is characterised by an enormous dilatation of the blood vessels. The capillaries of the papillary body, as well as of the cutis proper, are all distended, as if by a forcible artificial injection. The cutaneous vessels, from the lower cutis margin onwards, are almost all of equal calibre. This is best observed in very thick, well stained, well cleared sections. The wide net of blood vessels can then be followed everywhere, and the absence of an adequate dilatation of the lymph vessels and spaces determined. The fact that this great dilatation is found everywhere, even on pieces taken from the cadaver, while we do not see it, under similar circumstances, in many erythemata, points to a maximal vascular paralysis at the height of scarlet fever, whose influence neither the agonal spasm nor the depletion of the skin can overcome.

In view of this very great vascular dilatation and the absence of all signs of marked œdema, we must ascribe the puffiness of the scarlet fever skin mainly to the over-filling with blood. It is well known that after the disappearance of the exanthem, with or without simultaneous nephritis, an œdema is readily developed in the skin. But this is not a symptom of the scarlet erythema; it is an independent condition, probably a neurogenic œdema of toxic origin (see œdema).

Nor can we speak, in scarlet fever, of a true (Cohnheim's) inflammation with necessary emigration of white blood corpuscles. Indeed, it is remarkable how few white blood corpuscles are found, hardly more than in the normal skin. Towards the end of this period, along with still dilated vessels and commencing scaling, we certainly find more nuclei around the vessels and in the whole papillary body. But a good protoplasm stain shows that they only belong to stationary connective tissue cells. These never secrete much stainable protoplasm; there are never plasma cells in scarlet fever. Mast cells are also rare; some are found in the scaling stage. Finally, there are only a few wandering cells in the epithelium. Simply considering the changes in the cutis, we would therefore be in doubt whether we were dealing with an inflammation, or only with a vascular paralysis. To decide this question we must consider also the changes of the epidermis.

At the acme of the eruption we find, in the compressed prickle layer, no particular changes; in many preparations the nuclei are particularly well-stained, and frequently there is a slight dilatation of the nuclear cavity; consequently the visible symptoms of the changes, as evident in the prickle cells, are limited to a slight peri-nuclear œdema. Especially notable is the complete absence of mitosis, and of any dilatation of the inter-epithelial lymph spaces. There is neither œdema nor proliferation of the uncornified epidermis. Mitoses are found first, and pretty numerously, in the stage of scaling.

We first find distinct changes in the transitional layers and in the horny layer itself. In different cases and in different parts of the skin the appearances vary, but are based on two main typical forms.

Either there exists, as before, a well-marked granular layer, and we have consequently an absence of staining of the nuclear remains in the horny layer above. Then only the latter is pathologically altered; it has as a whole the appearance of the basal horny layer, is homogeneous, stains deeply in acid colours, and frequently has a shining cut surface, like the substance of the nail. The usual loosening from the basal layer to the middle layer, and the hardening from that to the terminal layer are absent. The normally triple horny layer has become one. This may be called the *callous type.*

Or, the granular layer has disappeared, or is reduced to small fragments, and then the rod-like remains of the nuclei are preserved in the incompletely cornified mass. This latter is more loosely constructed, and its upper collections of cells scale irregularly, the prickle layer passing directly into the scale. This type may be distinguished as the *mucous membrane-like* type of the horny layer.

Pieces excised at the stage of desquamation show the following: in the first type, the homogeneous, callous horny layer is elevated by a

loose horny layer, of the structure of the normal, central layer. Then comes a new, normal basal layer, and the granular layer.

In the mucous membrane type, the loose horny layer, with rod-shaped nuclei, gradually passes into a firmer basal layer, and then comes, here also, a granular layer.

The callous type is the more frequent in scarlet fever, and so far the more characteristic, as it leads to the separation of larger scales. It represents, from the commencement, a drier and firmer epidermis, and is therefore always found on the palms and soles. The mucous membrane type is much rarer (it resembles the scaling in psoriasis, eczema, &c.); it points to a greater moisture and softness of the epidermis, and in desquamation produces smaller, irregular scales. This type usually passes later into the same form of scaling as the first, so that we find, on the surface, a looser horny lamella, with rod-shaped nuclei, in the act of being thrown off, and underneath it again a normally cornified, firmer horny layer. This corresponds to clinical experience; when scaling sets in immediately on the disappearance of the eruption, the scales are usually smaller and softer, and only gradually become larger and firmer.

The scaling may lead to a great reduction of the prickle layer, so great, that the horny layer, although desquamating, appears the thicker. Further, one finds no mitoses in this reduced prickle layer, and it is evidently associated with persons of low vitality, who, perhaps on that ground, succumbed to the fever. In other cases, on the contrary, we find, in spite of the scaling, a remarkably broad prickle layer, even containing mitoses, though not in great numbers. The reproduction after the scarlatinal process is evidently slow. These are the same cases, at the commencement of desquamation, which, even in the cutis, show more connective tissue cells than normal around the vessels and in the papillary body.

To sum up, we have in the cutis a maximal amount of congestion without any distinct œdema; only in the stage of scaling are the upper parts of the skin more cellular. In the epidermis we find, even in the stage of full development, a parakeratosis, which later, in different ways, leads to scaling, while the prickle layer shows neither œdema nor emigration. It cannot be denied that in this apparently contradictory conjunction lies an important criterion of the scarlet fever process. The anomaly of cornification points to an abnormal saturation of the whole epidermis, although the ordinary signs of an œdema of the prickle layer are absent. Does this depend on the vascular paralysis? The cutis also is sodden, although we cannot recognise any actual œdematous spaces.

This question would be difficult to answer, had we not had the

opportunity of comparing the erythematous and the non-erythematous skin in scarlet fever, from symmetrical areas (*e.g.*, from both legs). There we see, that on the non-erythematous skin there is exactly the same parakeratosis of the epidermis, although perhaps in somewhat lesser degree, as in the scarlet redness, and it must also have been sodden, since the folding of the over-stretched epidermis is just as distinctly marked. But there is none of the excessive amount of hyperæmia of the erythematous parts. That, I think, definitely establishes the fact that the vascular paralysis is only an accompaniment and not the cause of the parakeratosis, although it may increase it. It is evidently a general vasomotor disturbance at the height of the infection, which depends on lesions of the higher vasomotor centres, and complicates, in different degrees, the other changes. In scarlatina, without eruption, we have also parakeratosis, without vascular paralysis.

What significance have the deep red points, which appear as the first symptom of the eruption, and, if they do not disappear in the diffuse erythema, give to it its punctate appearance ?

I believe that these points correspond to localised areas of greater hyperæmia, such as I have occasionally found in scarlatinal skin. At these places the sub-epithelial capillaries were dilated to their maximum. The papillary bodies of these small areas, corresponding to a few papillæ, were abnormally cellular, but contained only a moderate number of leucocytes, and no red blood corpuscles. Nevertheless the cellular connective tissue showed that these places did not correspond to any agonal or post-mortem creations. The epidermis over them was diminished, the prickle layer a mere thin stratum, with horizontal rod-shaped nuclei, and the horny layer scaling. It is therefore only a punctiform increase of the vascular paralysis and the parakeratosis present in the neighbourhood, possibly corresponding to the first embolisation of the skin with the scarlatinal poison.

That these extremely congested areas pass easily into true stasis, and may therefore form the starting point for cutaneous hæmorrhages, such as are often present in scarlatina, is very likely ; but I have not yet had the opportunity of examining them. It must be borne in mind that the petechiæ of scarlatina are the result of a paralytic, congestive hyperæmia, while those of measles result from stagnatory hyperæmia.

The small, watery vesicles and the larger pustular blebs, which sometimes complicate scarlatina, still lack histological explanation. The epidermic changes described by Neumann (œdematous spaces, epithelial fret-work, blood extravasations, exudation cells under the horny layer) are too indefinite. They in no way correspond to the ordinary appearances of the scarlatinal skin, as we must regard it, if it has to form in any way the type of the dermatitis in scarlatina.

And the contrast which Neumann puts forward between scarlatina and measles, that the poisonous action is especially limited in the latter to the glands and vessels, in the former to the epidermis, owing to which the scales are infectious in scarlatina and not in measles, is quite insufficient, and only proceeds from the old, erroneous view that the papule of measles was a follicular inflammation. The main difference in the action of the poison in the two processes is, that in scarlatina we have a pure paralysis of the vessels, while in measles we have concurrent and dominating spastic appearances of stagnation; the ordinary appearances of inflammation in both are very slight; in greater development, they are exceptional and local. The epidermic changes are much more easily explained as direct specific actions of the poison, than as the banal results of a simple dermatitis. Were they only the latter, the scaling in scarlatina, corresponding to the lesser exudation in the lymph spaces of the cutis, would be less than in measles, while it is exactly the opposite. This latter point forms the most pregnant histological contrast between the two conditions, the fully dilated blood capillaries, without dilatation of the lymph vessels, in scarlatina, and the large lymph spaces and canals, along with narrow blood vessels, in the post-mortem skin of measles.

Certainly this last statement is only true of the typical cases. Exceptionally (one of my seven cases) there is, even in the scarlatinal skin, an interstitial œdema of the cutis, with dilatation of all the lymph spaces, especially around the follicles, though it is rare and patchy. There might then be a similar condition of contraction of the vessels, as normally in measles. In life, such a case, with tiny projections of the skin, would represent the so-called scarlatina papulata.

Then it is not unimportant, in order to avoid misconception, to note that the appearances here described are only exactly true of older children and adults. Anyone examining the skin of an infant, dead from scarlet fever, will find the number of cells in the cutis very considerable. But it is not much greater than we find normally in the skin at this age, where the cellular parts play a greater rôle than the collagenous. This is equally true of all skin diseases in infancy, but they are more rarely examined than the acute exanthemata.

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Varicella.

Chicken-pox appears in the form of rounded or acuminate vesicles, which appear rapidly on very reddened bases, with clear, occasionally somewhat cloudy, non-purulent contents. They are very superficial, project over the level of the skin, and show in the centre no depression. After lasting one or two days they dry up. After the falling off of the small brown crust, there remains only rarely a slightly depressed, smooth, soft, non-pigmented scar; usually they leave no trace.

I take the description of the eruption from a characteristic "chicken-pock" which I excised from an eight-year-old boy, on the second day of its existence. I choose this because it gives the most perfect contrast to the centrally depressed variola vesicle, for in it the most central point of the surface is the most elevated. It has a tent form; the lateral walls rise obliquely from a broad base, towards the centre of the covering, which is formed by a few stretched, horny scales. From these, cellular partitions radiate downwards, as in small-pox. The chicken-pock is consequently divided like the small-pock, but the point where the septa join lies here, not in the centre of the base of the pock, but on the covering. The cavity proper only occupies the upper part of the much widened prickle layer. It is limited beneath by the deeper strata of the prickle layer, mostly pathologically altered. In the centre, the cavity extends deeper, to the level of the papillæ, which, swollen and enlarged, and covered only with one or two layers of altered epithelium, project into the cavity. The inter-papillary, epithelial processes remain, on the contrary, mainly intact, both in the centre of the chicken-pock and in their deeper layers, and here and there even show normal mitoses. Laterally the cavities are bounded by epithelia, sometimes swollen and elongated, sometimes compressed; the margin is pretty sharp and is only slightly interrupted, at certain points of the circumference, by small secondary cavities, which develope from colliquation of individual epithelial cells. The cover of the cavity is formed by the scale already referred to, which consists of the original horny layer, with the addition of a few layers of compressed transitional epithelium, with rod-shaped nuclei. Both these and the septa of the cavity take, with acid colours (picric acid, acid orcein), the same stain as keratin and fibrin; when treated by Wiegert's method only the latter give the reaction of fibrin and of fibrinoid degenerated epithelium, while the compressed epithelium of the covering retains the acid stain; it has therefore not undergone fibrinoid degeneration. (Front., Fig. 10.)

The colliquative changes of the epithelium evidently deserve the greatest interest; for—Zoster excluded—we nowhere find them so

typically and perfectly developed. In small-pox, to which almost all studies on this point have been limited, the formation of pus soon obscures all other changes, and especially arrests the phenomena of coagulation. I would therefore recommend varicella for future use, as the prototype of fibrinoid degeneration of the epithelium.

The softening of the poisoned epithelium, and the secondary coagulation of the albuminoid bodies, set free from the epithelial protoplasm, take place in two quite different ways. In the one form of colliquation, which was first described by E. Wagner and Wyss in small-pox, and more particularly by Leloir and myself in many bullous processes, the protoplasm swells inside the cell, while the nucleus and the cell membrane at first remain unchanged. This stage of *cellular œdema* may be followed by a direct and *total solution of the cell body*, which is thus dilated to a large cellular cavity. The resulting coagulation now leads only to a sparing, fine granular precipitate, which lies on the well-preserved nucleus, or on the thin, distended, but also well-preserved cell wall. After the liquefaction we find the nucleus either at the base of this cellular cavity or fixed somewhere inside, in the fine coagulated threads, or washed away in the rupture of the cell wall. At first it still has the staining reaction of a healthy nucleus, then it stains more faintly, and finally it also takes a very pale fibrin stain. Or, instead of total liquefaction of the cell body, it is only *partial*, trabeculæ of firm protoplasm running between. If coagulation now sets in, the enlarged cell has a reticular structure. The remaining protoplasmic trabeculæ coagulate into a net-work, uniting nucleus and mantle substance, and often radially arranged, while the intermediate, already liquefied parts supply a granular, fibrinous precipitate, which is deposited on the net-work. In this case also, nucleus and mantle remain relatively longer preserved, and take more and more the characteristic fibrin stain.*

I call this form of degeneration, which as yet is the only one described, "reticulating colliquation," in view of the most frequently recognisable stage of the fibrinous reticulum.

But in the fibrinoid metamorphosis of the epithelium there is a very different form, which is especially well-developed in Varicella

* On account of the importance of the matter, I may be allowed a few technical remarks. Weigert's excellent method for the recognition of fibrin is not sufficient by itself, where it is necessary to demonstrate, at one time, coagulating, coagulated and normal substances of firm character (nuclein, keratin). In such circumstances I recommend the following double stain. For the recognition of keratin along with fibrin, previous staining with picro-cochineal or orange-cochineal and then with Weigert's stain; for the exact separation of healthy from already œdematous and from actually coagulated cells and nuclei, previous staining with acid orcein (elastic stain), followed by methyl blue with decolorisation by glycerine ether mixture. Only fibrin, keratin, collagen and elastin retain the orcein stain.

(and in Zoster). There is no sharp separation between mantle and cell contents, and consequently no isolated liquefaction of the latter. The whole protoplasm rather swells up and becomes cloudy and opaque. These swollen epithelial cells become rounded, just as those affected by reticulating degeneration, and lose their normal prickles, which, evidently withdrawn by the cell protoplasm, pass into the enlarging surface. The thus swollen protoplasm assumes a tough, soft, very plastic consistence, and yields to every impulse. According to their position, the cells are therefore round or flat, biscuit-shaped or pointed, or, finally, drawn out, in the septa, into long bands. While these mechanical changes are going on in the softened protoplasm, it gradually takes on the colour reactions of fibrin, though never completely, and in rare cases not at all. With the orcein methyl-blue stain, for example, some of these completely swollen cells show an intense blue colour and fine granulation of the cell body. This second form of colliquation is consequently not so radically destructive as the reticulating degeneration, and appears in its initial stages to be capable of restitution. This is also likely for another reason. During colliquation of the cell body to a soft, extensile mass, progressive changes go on in the centre. The nuclei divide in almost all those swollen cells, without any previous mitosis, simply by constriction. There are found two, four, eight, sixteen, even thirty-two and more nuclei, of an epithelial type, inside these cells, which swell up to a corresponding degree. With the stain mentioned, there can be no confusion with wandering cells. The nuclei are faintly stained, vesicular, contain chromatin mainly only at their periphery, and are flattened by lateral pressure (facetted). They always lie together in the centre of the cell, either closely surrounded by a thick wall of degenerated protoplasm, or separated from it by a space filled with fluid, a nuclear cavity. That these nuclei have not developed mitotically is quite certain, for, in the neighbourhood of the vesicle, mitoses are present in enormous number, and are very clearly seen with the same methyl-blue stain. In view of the acute course of the affection, mitoses would be evident in the centre of the swollen cells, if they were present. Thus these colliquated cells assume the form of peculiar giant cells,* and there is evidently complete independence between the degenerated protoplasm on the one hand, and the proliferating nuclei on the other. We see, not infrequently, fibrinoid degenerated cells drawn out into bands, which, in place of the nucleus, have a collection of (4, 8, 16) well-formed nuclei. Most of the cells, however, have the form of hollow spheres or balloons; only with imperfect nuclear staining † could one regard them as completely dead necrotic masses. In

* Perhaps the giant cells noted by Luginbühl in small-pox.

† *e.g.*, after hardening in bichromate of potash.

view of the predominance of these balloon-like giant cells, I call this whole process of fibrinoid degeneration, " ballooning colliquation."

It is self-evident, that the reticulating colliquation mainly attacks the older, the ballooning, the younger epithelium, for, as the age of the prickle cells increases, a firm, marginal layer separates from the rest of the protoplasm, in preparation for cornification. On the still homogeneous protoplasm of the younger epithelia, the colliquation induces a homogeneous swelling and coagulation. They undergo degeneration more slowly ; the greatest destruction by reticulating degeneration is found in Varicella, as in all vesicular diseases, in the upper prickle layer.

The varicellous process consequently commences with the reticulating liquefaction of a few prickle cells of the central and upper prickle layer, in the middle of the first appearing congestive spot. The completely liquefied, confluent cavities rapidly dilate to form the vesicles, the persistent non-liquefied epithelium is compressed to form the septa, as are the cells above to form the cover. While this septate cavity chiefly enlarges by swelling upwards, the ballooning colliquation proceeds in all the epithelial cells of the base, especially at the centre of the pock, then at the lateral margin, and in all the healthy epithelial cells of the centre. Even the septa, which run through the vesicle, are therefore frequently surrounded by ballooned giant cells. At the base of the chicken-pock the balloons form a loosely connected covering, which runs over the central papillary apices, often only in a single layer. Laterally, these ballooned epithelial cells pass into simply œdematous epithelium of normal form and size, often, however, showing two or more constricted nuclei. There is no coagulative necrosis, in Weigert's sense, in varicella. (Front., Fig. 12.)

The contents of the vesicle, at the height of its development, consist of finely granular coagulated fibrin, enclosing a few fibrinously degenerated, compressed, or ballooned epithelia, and almost no wandering cells. Only a few wandering cells permeate the epithelium of the base and the surroundings. The regular formation of mitoses, all round the vesicle, guarantees the scarless cornification, which normally distinguishes varicella.

While these processes are going on in the epithelium, the cutis only shows a marked dilatation of the vessels, a moderate serous saturation, and a not inconsiderable enlargement and multiplication of the cells around the vessels (a certain number of mitoses are found) ; while the emigration of white corpuscles is reduced to a minimum. The younger perivascular cells have, some of them, the character of spindle cells, others are rounded, and among them we find, especially at the periphery of the eruption, single plasma and mast cells.

The acuteness, which distinguishes the varicellous process, is evident histologically (in distinction to small-pox), in the relatively large, slightly septate cavities, due to the rapid distention of a few liquefied cells. Notwithstanding its appearance, the chicken-pock is certainly not monolocular. Its thin covering and superficial position result from rapid formation, as the time is too short for the application of many compressed epithelial layers to the horny layer, for the development of a thicker covering. The non-purulent character of chicken-pox is histologically very pronounced. Its benign, unscarred course is explained by the superficial position, the absence of purulent infection of the pustule, and the early repair by young epithelium, indicated by the numerous mitoses around the cavity. The absence of a dimple results from the acute, abortive course of chicken-pox, which does not permit the formation of a swollen peripheral zone of reticularly degenerated and very œdematous epithelium.

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Variola.

Small-pox passes regularly from a papular into a vesicular and pustular stage. The papule is at first the size of a mustard seed, and surrounded by an inflammatory halo. On the third day the vesicular nature becomes evident; the papule becomes transparent at its point. While it slowly swells to the size of half a peppercorn or a split pea, the summit flattens, and remains depressed in the centre. At the same time the contents become cloudy, the base of the vesicle œdematous, and neighbouring vesicles run together. On the fifth or sixth day the vesicles are distinctly purulent, and still more swollen, while the central dimple is usually once more flattened out; some pustules rupture and discharge a viscid, yellowish fluid, which rapidly dries up into a crust. From the tenth day onward the pustules dry up, either directly or after rupture, while the œdema of the cutis diminishes. After two or three weeks the thick scabs fall off, and leave behind them, at first, swollen, often deeply pigmented scars, which are gradually transformed into deep white scars, with sharp borders. On the palms and soles, and in general under thick horny layers, there are no elevated pocks, but only deep red, flat eruptions, transparent in the centre, and a peeling of the thick horny layer.

The main character which distinguishes the vesicular formation in true Small-pox (Variola, Varioloid) from that in Chicken-pox, consists, on the one hand, in the slow growth, on the other, in the prompt addition of suppuration to the fibrinoid degeneration, which obscures the effects of the latter.

Here also the cavity formation begins, even in the papular stage, in the upper prickle layer (Rindfleisch) by reticulating colliquation of

the œdematous epithelium. But owing to the slow advance of this colliquation, epithelial complexes, for some distance, are compressed above and between the primarily liquid parts, and thus part of the cavity is, from the commencement, pretty regularly divided by trabeculæ or septa, perpendicular in the centre and directed somewhat outwards at the side, into a series of smaller segments; on the other hand, the covering is considerably thickened by compressed layers of epithelium.

At the same time the epithelium of the lower prickle layer undergoes ballooning colliquation, not only at the apices of the papillæ, but even in the depths of the ridges, and, indeed, for some distance down, in the cells of the prickle layer of the hair follicle which penetrates the pock. The balloons which develope are in general smaller than in Varicella, seldom more than two or three times the size of an ordinary epithelial cell, and they consequently show much less tendency to nuclear fragmentation. Balloons with two nuclei are very common, with four rare, and with more (20-30), quite exceptional. Actual epithelial giant cells, such as are found in numbers in Varicella, are very rarely observed in Variola. But otherwise the ballooned epithelium resembles that of Varicella. The cells are disconnected, from loss of their prickles, and thus form a loose collection, which covers the swollen papillæ, fills the whole base of the pock almost to half the height of the widened prickle layer, and extends, along the hair follicles, into the depths of the skin. (Front., Fig. 13.)

As the pock extends peripherally, this storeyed formation, this separation into an upper and lower half, continues. In the upper part of the prickle layer, the cavity extends laterally, many of the œdematous marginal epithelial cells liquefy, some retaining web-like remnants of coagulated protoplasm, others completely, and on the rupture of their thinned walls, communicate with the main cavity. In the under part, on the contrary, the ballooning colliquation does not extend so rapidly, rather giving place to simple cellular œdema, and further to mitotic epithelial proliferation. At the periphery, consequently, the cavity is more superficial than in the centre; the margins of the cavity rest on a solid cushion of swollen and partly proliferating epithelium.

Thus it is that, at the height of development, the cavity of the pock has the form of a mushroom, the main cavity formation taking place in the upper projecting parts (Rindfleisch's Pockenhaube), while its under half is sharply constricted. These two divisions differ in their origin, since the cavities in the upper segment are intra-cellular, in the lower, inter-cellular; in the one they arise from the over-distended, liquefied and ruptured cells themselves, in the other they only re-

present the hyper-distended lymph spaces, between the loose ballooned epithelia. We can, therefore, scarcely speak of a uniform cavity in the under part of the pock, but rather of a network of wide spaces and canals, communicating above with the cavity proper.

The transition of the swollen, cushion-like base at the periphery, into the zone of ballooned cells in the centre of the base of the cavity, is very gradual, the partly hyperplastic, partly œdematous epithelial cells of the periphery showing, on the one hand, a few mitoses, on the other, simply constricted nuclei, and separating as they become rounded. Their transition into the sub-cavities of the pock also takes place gradually, partly by reticulating colliquation and further advance of the cavity downwards, partly by ballooning degeneration, whose products then lie loose at the base of the peripheral supplementary cavities.

Finally, there is also a very gradual transition of the ballooned cells of the base of the pock into the flattened cells of the compressed cords and processes of the cavity, and also from these into the compressed epithelial layers of the covering, and into the fine, fibrinoid epithelial remains, which persist between the reticularly colliquated cells of the cavity proper.

The whole of the colliquated and the greater number of the compressed epithelial cells now gradually undergo fibrinoid transformation, to a much greater degree than is the case in Varicella. Only the compressed epithelial cells of the covering, and the thickest compressed cords, so far as they are not in direct connection with the cavity, escape, as does the œdematous epithelium at the periphery of the base of the pock. While in the compressed cords usually only the protoplasm shows the fibrin reaction, the nuclei frequently retaining their normal reaction, the nuclei of the ballooned epithelia of the base degenerate over a much greater area than in Varicella. They have consequently been regarded by many investigators as "a-nuclear fragments," but, even if their fragmented nuclei show the fibrin reaction, their outlines can always be demonstrated. A-nuclear masses are in no way a necessary primary constituent of the pock, much less the primary appearance (necrosis), of pathognostic significance, on which depend all the other inflammatory changes. The ballooning of the epithelium is rather only one of the degenerations which accompany the inflammatory appearances, and if the nuclei gradually lose their staining power, this is only a secondary, not particularly important event. We might as correctly (viz., from the gradual loss of nuclear staining power) describe many compressed cords of the cavity as a-nuclear masses.*

The external configuration of the pock, the much discussed um-

* "Kernlose Schollen." Hardening in bichromate of potash and then in alcohol makes it much more difficult to demonstrate the nuclei in ballooned epithelium.

bilication, is simply explained. We must admit that, where a hair follicle accidentally runs through the centre of the pock, a form of depression may be produced, for the swelling of the prickle layer will here be limited by the cornified neck of the hair follicle, which, like the old horny layer of the surface, usually takes little part in the swelling. But these exceptional cases do not explain the characteristic central depression in the vesicular stage of the pock. The macroscopical result of the epithelial distension evidently depends on two changes—reticular colliquation and œdematous swelling of the epithelium. For only these two conditions lead to such marked increase, that their presence can be noted by the naked eye. Ballooning colliquation leads only to a very slight increase. If we thus compare, histologically, the differences at the centre and at the periphery, we find that in many pocks the reticulating degeneration at the periphery is greater, sometimes very much greater than in the centre, where the ballooning colliquation predominates. But, where the latter has once started and affected many epithelial cells, there is little room for reticulating degeneration. In such pocks we find, in the centre at the base of the pock—first, a very thick layer of ballooned epithelium, and above this closely set, compressed epithelial cords, between which there are small spaces produced by reticular transformation. In such pocks the umbilication is to be attributed to the distribution of the different kinds of colliquation. But these are by no means the pocks in which umbilication is most marked. These are rather found, where a special swelling of the periphery of the pock, due to great development of the œdematous and proliferating cushion, is added to the arrest of the process in the centre. And further, we also find distinct umbilication in vesicles, where reticular colliquation is equally developed over the whole pock, but excessively œdematous changes elevate the lateral parts.

The umbilication is therefore to be ascribed, in the vesicular stage of the pock, partly to reticulating degeneration, partly to epithelial œdema, of which the former is frequently especially developed at the periphery, the latter always limited to the periphery alone. The less swollen centre simply remains behind; it is not possible to ascribe to the perpendicular epithelial cords the function of guy ropes, for they are not capable of any mechanical strain, and when the pock is further distended, in the pustular stage, they at once give way.

How great the pressure of the lateral œdematous cushion is, we see by the fact, that underneath it the papillæ are gradually obliterated, while in the centre of the pock, up to the stage of suppuration, they not only persist, but usually project, swollen and œdematous, into the cavity of the pock. This deformity of the base is most marked in the pocks of the palms and soles. Here the stiff horny covering prevents

the projection of the distended prickle layer, and this therefore digs down into the cutis, here also especially at the periphery, for here the lateral cellular œdema is excessively developed. The pocks here are, not only beneath, but completely surrounded peripherally by a solid body, consisting, solely, of œdematous epithelial cells.* The cutis under this pressure softens towards the single point of less tension, the centre of the pock. Here, in the centre, the papillary body projects into the cavity (Weigert's "untere Delle"), and its papillæ are abnormally swollen, as if sucked up with a bleeding cup. It is hardly possible to find a more instructive example of the different conditions of pressure in the centre and at the periphery of the pock.

The best example of the opposite condition is supplied by those rare vesicles in which, even in the centre, reticulating colliquation reaches to the base of the pock. Here, of course, no depression can very well be formed.

During all this vesicular stage, the dilatation of the vascular cone, in relation to the pock, is proportionately slight, and the emigration of leucocytes strikingly small. But a good protoplasm stain shows, in the adventitial sheaths of the blood vessels, definite changes, viz., a dense collection of large plasma cells, which constantly increases as the vesicle matures. This abundance of plasma cells, which usually accompanies chronic infectious inflammations of the skin, is very remarkable, in view of the short time available for its formation. Such a well-developed plasmoma is only found, among the pock-like processes, in Variola itself, and points, on the one hand, to an exceptionally active poison, but on the other also to a relative deficiency in fluid, such as distinguishes the commencement of the variolous process (Pincus' infectious anæmia). The plasma cells show certain peculiarities. They are pretty regularly rounded, and often permeated by unstained spaces, which show the distended but empty net of spongioplasm. Their amount of granular protoplasm consequently does not correspond to their (considerable) size, and they rather give the impression as if the protoplasm, formerly present, had been washed out. But there are no fragments of protoplasm around them, and consequently no nibbled edges; they do not undergo the breaking up, so frequent in the chronic granulomata. Mast cells are only present in small numbers at this stage.

But the appearances completely alter from the fifth day onwards. The blood vessels are now distinctly dilated, not only on the surface, but through the whole cutis. A full stream of leucocytes, no doubt attracted by the germs lying dead in the tissue, runs through the whole cutis, and reaches, in the papillary body, such a density, that even in

* See below on the "Pockenkörper" of the palms and soles.

the thin sections the margin between cutis and prickle layer is hardly recognisable. At the same time, they fill the spaces between the ballooned epithelial cells of the centre of the pock, as well as between the œdematous epithelial cells of the lateral cushion, and there commences an ever increasing infarction of the cavity proper, which previously contained loose, fibrinous coagula, with white corpuscles. This reaches its acme in a few days, either, if the firmness of the horny layer hold, until the whole pustule is completely filled with white blood corpuscles, and thus converted into an almost solid tissue, or, if the horny layer yield, in a more or less profuse suppuration, which, according to external circumstances, lasts for a time or rapidly concludes with the formation of a crust. While the spontaneous pustulation at the end of the first week may, without doubt, be attributed to the poison of the disease itself, we must certainly ascribe prolonged suppuration to the addition of pyogenic organisms. With the spontaneous arrest of suppuration, towards the middle of the second week, the pustule normally dries up, and is completely converted into a scab.

Then healing commences. Even before the contents of the pustule are completely dry, a thin layer of epithelial cells, lying close on the connective tissue, extends, from all sides, under the pustule. This epithelial border contracts, like an iris diaphragm, and cornifies on its upper side, so that the original pustular contents appear to be surrounded on all sides by a horny capsule. It is of great importance for the future form of the scar, that the ingrowth of the young epithelium should take place in a level or usually somewhat convex surface. This is only possible, by the papillæ, which at the acme of the process project into the cavity, becoming flattened and even depressed by the increasing pressure in the centre of the papule. When the scab is thrown off, there is displayed a persistent trough-like depression. Where the scab, be it from a less extensive epithelial degeneration or from a smaller amount of pus in the cavity, does not so much depress the base of the pock, the papillary body is not so completely flattened out, and there developes no such striking, deeply excavated, smooth scar. Suppuration alone causes no necrosis of the papillary body, but it may, if profuse, lead to more rapid casting off of the scab, and thus indirectly to the freeing of the base of the pock; the profusely suppurating cases of small-pox are not those which leave the worst scars. No doubt prolonged suppuration, coupled with inappropriate treatment, scratching, &c., may lead in many places to a purulent sequestration of parts of the cutis, and thus to distinct scar formation. The depth of the scar consequently depends on the degree and the duration of the flattening of the base of the pock beneath the pustule and the scab,

and we see therefore that the rational treatment to avoid scars should be mainly directed to the aborting of the pustular stage, and the rapid removal of the scab by profuse epithelial new growth.

While the pustule is being converted into a scab, the masses of pus cells, which saturate the cutis, are rapidly absorbed. They withdraw into the lymphatics around the blood vessels, and are, further, especially in relation to the coil glands and their ducts, which frequently show dilatation and contain pus cells. The capillaries of the surface, as far as the scab has extended, are usually much dilated. After the falling off of the scab the epithelial proliferation often extends, and leads first to a thick epithelial mass, which flattens out the depression, and ultimately gives place to the thin epithelium of the scar. For a long time the blood vessels and all the lymph spaces of the cutis are dilated, and wandering cells and pigment are more abundant than normal. The elastic tissue suffers as little from small-pox as the collagenous.

Now that we have described the important process in its main elements, we must, in order to define our position towards them, discuss a few particular points which have played a certain rôle in the abundant literature of the subject.

The most important is the nature of the *epithelial degeneration.* Like most authors we distinguish two main varieties of degeneration, to which we have given the morphologically justified names: *reticulating* and *ballooning;* we regard both only as special forms of *fibrinoid metamorphosis.* They induce, in different ways, a fibrinoid, coagulated condition of the protoplasm of the epithelium, without producing a final stage, which, morphologically and tinctorially, completely corresponds with pure fibrin. It is certainly necessary to have a further definition, which comprises all the multiform, histologically very important substances, which develope from the combination of qualitatively different protoplasm, with different varieties and quantities of fibrinogenous lymph. Since the chemical changes are completely unknown to us, we can only classify them from their morphological peculiarities.

Our reticulating degeneration corresponds to the "Altération cavitaire" of Leloir and Renaut. But apart from the fact that the name "cavernous metamorphosis" is much too general, and can consequently never be adopted in German for this definite form of cavity formation, the definition is really too narrow. According to Leloir, the cavity formation invariably commences with a dilatation of the nuclear cavity, therefore a liquefaction of the endoplasm. But that is only occasionally the case. More often there are formed, in the œdematous protoplasm, in different places, sometimes around the nucleus, sometimes at the outer wall, small single vacuoles, containing fluid, which, if they run

together, leave a reticular frame-work, joining nucleus and cell wall. This undergoes fibrinoid degeneration and is covered with fibrinous granules from the intra-cellular fluid. On this ground I prefer the name "reticulating degeneration"; it comprises also the cases to which Leloir refers, in which the net gives way early in the neighbourhood of the nucleus, so that fine fibrinous threads hang from the greatly distended cellular mantle.

The important characters of the reticulating degeneration are different: the nucleus, and the cell mantle with its prickles, are long preserved.

Further, I can certainly not admit the explanation which Renaut gives of the *altération cavitaire* of Leloir, as the result of the penetration and multiplication of spherococci in the affected epithelial cells. We indeed find, in the lateral cavities of the pock, and in the peripheral cellular cavities near it, regularly distributed, round, deeply stained granules, Leloir's "protoplasmic dust." But these stain equally well with acid as with basic stains, and, under a high power, are neither so sharply margined, nor so regularly round as cocci, to say nothing of their different size. But it is still more important to know what they actually are. They represent a special product of the breaking down and coagulation of the epithelial protoplasm, but only of those cells *which are partly or completely cornified.* As long ago as 1878 I described this change as "nuclear degeneration," on account of the nuclear stain of the granules. In the description of the pocks of the sole we will discuss it in its fullest development.

Still less can I adopt the term of "*atrophy of the nucleus from dilatation of the nucleolus*," often used by French authors; if such a condition really exists, and is not a simple confusion with the well-known results of inappropriate hardening of the epithelium, it plays no rôle in the variolous process. Even the simple loosening of the nucleus in a relatively too large nuclear cavity is not to be directly regarded as a proof of cellular œdema, without reference to the accompanying conditions, for it may be influenced both by the method of hardening and by the tension and pressure inside the tissue.

The "ballooning degeneration," on the other hand leads to a comparison with the "cloudy swelling" and the "coagulation necrosis" of earlier authors. The reason we cannot adopt the view of Weigert, that the change of the cells in the centre of the base of the pock comes under the category of Cohnheim's coagulation necrosis, is clear from the description. On the one hand we miss the distinctive signs of that condition, the primary and complete loss of the nucleus, the absolute want of resistance to the surrounding tissue juices, and on the other, the ballooned epithelial cells possess a series of valuable

positive characters, which are ignored in the term "coagulation necrosis"; the common degeneration of the endo- and ecto-plasm, along with the inter-cellular bridges, the consequent separation of the cells from one another without any external force, the tendency of the nuclei to a-mitotic constriction, and the peculiar plasticity and alterations in form of the isolated cell bodies. Only when the nuclei in the ballooned epithelial cells can no longer be tinctorially differentiated from the protoplasm, therefore relatively late, have we before us what might be called (though with no special meaning) "a-nuclear masses." The compressed epithelial cords on the base of the pock go through exactly the same process of gradual colliquation and loss of the nuclear chromatin, without having acquired the type of ballooned cells. In short, I cannot admit an initial loss of nuclear stain, and since the ultimate loss of the nucleus cannot lead to a better distinction of the different varieties of coagulation, it has for me no special significance.

"Clouding" or "cloudy swelling" is described by most recent authors in the epithelial cells in the centre of the pock. Weigert's "a-nuclear masses" are supposed to develope from such cells, which are at first still nucleated and faintly cloudy, and then show irregular faint nuclear staining and greater clouding. The mesh-work of the pock, lying above, is also supposed to consist of cloudy a-nuclear masses.

Rather remarkably, Touton finds a zone of cloudy swelling in the neighbourhood of the pock, where, according to Weigert, proliferating cells are found. I suspect that the author had before him lateral parts of neighbouring pocks.

Renaut places "cloudy swelling" in direct contrast to the "altération cavitaire" of Leloir. The former is supposed to affect the cells of the base in the centre, and yet his cloudily swollen cells are by no means to be compared to the ballooned epithelial cells of other regions. For this degeneration begins in the perinuclear zone, and leads to colliquation, while the protoplasm in the ballooning degeneration is all altered together, and later undergoes, not colliquation, but thickening into a crust. Further, according to Renaut, the "putty-like ridges" between these cloudy cells persist, and are partly transformed into the septa of the pock. Now, since "putty-like ridges" do not exist in epithelium, he evidently means the neighbouring cellular mantle and inter-cellular bridges. But where these persist, we are not dealing with ballooning degeneration, but either with reticulating or with total liquefaction of the cell; the latter never occurs, the former only exceptionally, at the base of the pock. Thus I cannot adopt Renaut's "cloudy swelling."

Finally, Pincus, who has very thoroughly studied, not small-pox,

but vaccine pustules, also finds, under the inoculation zone, a zone of "cloudy swelling," which he believed to be produced by three factors: diminished action of the poison, lesser irritation, and specific infectious anæmia. The nuclei are either normal or shrunken, but not broken up. Pincus regrets the want of accord in the nomenclature, but does not improve matters when he proposes to use the name "coagulation necrosis," although the cells have well preserved nuclei, are not dead, and are not soaked by the tissue stream, as dead cells are.

It is thus clear enough that the description "cloudy swelling" does not take us very far. Tempting as it may be, it is a dangerous tendency to introduce the definitions of general pathology into our special studies, when the definitions are not sharply defined and definable, as, *e.g.*, cloudy swelling. Coagulation necrosis, reticulating and ballooning degeneration of the epithelium are sharply defined terms, and only lose in crispness when approached to "cloudy swelling."

Finally, it is to be noted, that the comparison of the ballooned epithelium at the base of the pock with diphtheritic (Weigert's diphtheroid areas) and croupous (Leloir) metamorphosis does not advance us, for it is not so clearly defined as our term. And we must be all the more careful not to use these very terms for the ordinary pock eruption, for there are diphtheritic and croupous pocks, which present quite other appearances. These degenerations also come under the category of fibrinoid metamorphosis, but are distinguished from the ordinary degenerations of small-pox, by the greater degree of coagulation and by the complete and sudden loss of individuality of the separate cells. Of the many pocks which I have examined, there was only one which showed a distinct streaky, croupous metamorphosis of the base. It affected certain papillæ and adjacent basal epithelial cells, which partly formed the base of the cavity, partly the attachments of the septa. The metamorphosis extended directly from the connective tissue to the epithelium, although the margin between the layers could be distinctly recognised by good staining, for the nuclei of the croupous epithelial cells were still pretty numerous; the nuclei always lay in the interstices of the vitreous, shining, homogeneous, reticularly degenerated product, which, on differential staining, showed fibrinoid and not hyalin reaction. In the vicinity of the ballooning degeneration, small balloons lay in ever thinning, net-like clasps, of a croupous nature, indicating that only the inter-cellular bridges and a fine external layer of the cells were concerned in their formation.

Similar limited diphtheritis of the papillary body, along with croup of the adjacent epithelium, may be found in very different processes—*e.g.*, initial sclerosis, ulcus molle; it has consequently no special significance in the variolous process.

We owe to Renaut and Pincus the important proof, that a short *initial stage of anæmia* precedes that of hyperæmia in Small-pox (and Vaccinia). Renaut ascribes it to a simultaneous œdema, with ectasis of the lymph capillaries, Pincus regards it as a direct action of the infection. Since we know from Measles, that the infection in the acute exanthemata may induce, not only vascular paralysis but also spasm of the arteries and the veins, both views have their justification; only the view of Pincus appears to be more correct for the ordinary cases, since we rarely see signs of spastic œdema in young pocks. But the conditions of spastic anæmia and spastic œdema are nearly related, and readily pass into one another.

Both authors mention as a secondary and important phenomenon, a saturation of the cutis with lymph, which sets in at the commencement of the vascular paralysis and hyperæmia, and the distension of the already-formed epithelial cavities by the addition of lymph. With this we agree; but when Renaut attributes the small number of leucocytes in the epidermis to the filtration of the lymph through the basal epithelium, he makes clear that he has peculiar views as to the routes of the leucocytes into the epithelium (see also above, Renaut's "putty-folds"). No, the way lies open before them, but the power is absent. Only when the germs die, does the chemotaxis, which saturates the cavity with pus, begin.

Pincus describes, in the vaccine pustule, a primary *infective hyperkeratosis*, analogous to the primary infective anæmia, to which I agree, though certainly in the ordinary pock it is only just indicated. Wherever the horny layer, at the commencement of the process, has a considerable thickness, the basal horny layer swells up—as in Measles and Scarlatina—shows its cell contours, and is moister and not so greasy. At the same time the process of cornification, at these places, goes deeper, possibly only on account of the increased pressure of the œdematous horny layer, and the prickle layer is correspondingly thinned (there is, at present, no new formation). We find such appearances at the periphery of larger pocks, especially confluent ones, and on the skin between.

But this opposition of a pathologically accelerated cornification is more evident on those parts of the body which normally carry an excessively thick, coherent horny layer, viz., the palms and soles. This peculiarity gives to these pocks such a different form, that I must, in conclusion, shortly describe them, supplementing what I maintained in the year 1877. I noted then, that the seat of the degenerative changes in the pocks on the soles was much higher than usually believed—namely, in the basal horny layer, which swelled to ten or twenty times its ordinary width, and, from the appearance of rod-shaped

nuclei, preceding the degeneration, took on a more youthful appearance. This statement I can amply confirm from much more abundant material. But I was wrong in assuming this position of the cavity formation to be general in small-pox. It is indeed limited to these regions, and forms a very interesting variety of the ordinary pock.

In the smallest, just visible, mustard-seed vesicles of the sole, the basal horny layer is already swollen into a considerable, lenticular, transparent, solid body,* which is thicker than the other layers combined (the unaltered upper horny layer and the thinned and compressed prickle layer). Only at very limited spots in the centres of these eruptions, corresponding to the breadth of three or four papillæ, are the papillary body and the prickle layer much altered, and a communication of the horny "body" with the pathologically altered cutis established. For in general the "body," the foundation of the future cavity, rests in its whole extent on a healthy prickle layer. The base of the pock, which usually is only somewhat constricted like a fan, is reduced here to a very thin handle, on which the pock afterwards rests like a shell. Here only, at the very small base of the pock, is the material of the cavity the same as usual—namely, the prickle layer; on the sole and palm, the cornified and swollen epidermis provides most of the material for forming the cavity.

In a few cases, in spite of the difference of material, the cavity formation is as usual. We have in the upper part reticular, and in the lower part ballooning degeneration, and there are only three points —apart from the thick covering—by which these mature vesicles may be distinguished. Firstly, the whole pock is subjected to much greater pressure, and has, therefore, a very typical, symmetrical, fan-like form; then the cavity formation is always limited to a smaller central space, and there remain at the sides much greater masses of swollen epithelium—peripheral remains of the pock body—than usual; finally, under the pressure of this latter, the papillary body at the periphery of the pock is completely flattened, so that, as indicated above, the central papillæ are pressed upwards, and, enormously swollen, project into the cavity. So that, though superficial umbilication is always absent, deep umbilication is the normal condition.

But in other cases, after formation of the horny body, there is only very slight excavation at the base, between the ballooned epithelial cells of the short pedicle. The whole "pock body" then, in view of its horny character, undergoes a drier degeneration, which, at the first glance, has no resemblance to the ordinary process. But on more closely considering this cloudy, horny mass, we see that it also shows an extending fan-like formation and alternately vertical

* Pockenkörper.

or oblique streaks of substance, homogeneous or mixed with nuclear remains and staining granules. Especially directly under the covering of the pock, we see, with appropriate staining, perfectly homogeneous collections, regularly alternating with clearer looser ones. The latter are permeated by innumerable, finer and coarser, always dust-like granules, which take both nuclear and protoplasmic stains; they are swollen, horny cells undergoing "*nuclear degeneration.*" Especially in young pocks of this nature, we see that these granules have nothing to do with fragments of leucocytic nuclei, for leucocytes do not reach beyond the base. Nuclear degeneration then replaces, in these drier cornified pocks, the usual reticular degeneration, as it occasionally does in ordinary pocks.

Streaks of these "nuclear degenerated" epithelial cells extend from the covering to the base of the pock, intermixed with homogeneous, compressed, structureless, horny columns, which correspond to the septa of compressed epithelium in the ordinary pocks.

The ballooning degeneration at the base of the pock has also its analogue here, for the separation of the ballooned epithelial cells from one another is much less general than usual. There are formed collections, of rounded and elongated form, which are composed of several ballooned epithelial cells welded together. Thus we have, instead of a few firm septa and trabeculæ of compressed epithelium, with loosely connected masses of balloons between, a more regular net of swollen and compressed epithelium, enclosing a smaller number of loose balloons. In several of these pocks I have found, at the base, a croupous metamorphosis of the epithelium, but I do not wish to indicate it as characteristic of the dry pocks of the sole of the foot.

There are, of course, in addition to these extreme cases of "moist" and "dry" pocks of the palms and soles, transitions, in which, *e.g.*, in otherwise dry pocks, a little series of delicate, elementary vesicles appears underneath the covering, and so on.

The healing of the pocks of these regions, where the spots are, from the commencement, surrounded by healthy prickle layer, is usually rapid and perfect, although large masses of horny substance are cast off.

How much of the substance of the pock body is to be ascribed to the swelling of the old basal horny layer, and how much to new cornified layers, must be left to further investigation of this interesting primary infective cornification. At all events the "pock body" is not, as Weigert and Touton maintain, a late structure, destined for the encapsulation of the pock, but a body which is normally formed on the palms and soles, in which the degenerations chiefly, though not entirely, take place.

After this thorough discussion of the degenerative products of small-pox, we can express our views all the more shortly on the supposititious protozoa, which were first discovered by Pfeiffer and van der Loeff, and studied by the former, mainly in varioloid processes. They are identical with our ballooned epithelial cells; on this point Pfeiffer's drawings leave no doubt. Like Renaut's spherococci, which proved to be fragments of nuclear degenerated epithelium, the so-called protozoa, especially the cystic forms, are nothing but ballooned epithelium. I have chosen the latter name in view of this fundamental confusion; it indicates that, by fibrinoid metamorphosis alone, cystoid structures may develope from epithelial cells.

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Phlyctænosis Streptogenes.

The following important, and as yet unique case I owe to the great kindness of Dr Gläser.

Marie H., the one-year-old child of a Russian emigrant, took measles in Hamburg, and after its disappearance a fresh, universal eruption broke out on the skin. It consisted of small acne-like nodules, with slight peripheral redness; there was moderate fever. On the next day the eruption was more developed and profuse. On some nodules, small, circular, transparent vesicles, about the size of a pin-head and of a light grey colour, had developed. Head, chest, back and extremities were affected. There was nasal catarrh. The mouth and the pharynx appeared intact. On the third day of observation, the eruption still further extended, and the nodules partly became confluent. The vesicles increased; some of the spots showed definite umbilication. After the

occurrence of cutaneous hæmorrhages, bleedings from the nose and increased fever, the child died, collapsed, on the fifth day of observation.

At the *sectio*, the eruption was partly paled, partly bluish red. The mucous membrane of the lips and nose was excoriated, the tonsils swollen, the mucous membrane of the border of the tongue necrotic ; there were necrosis and excoriation of the epiglottis, hæmorrhages in the pleura, scattered broncho-pneumonic areas in the lungs, swelling of the follicles of the spleen, cloudy swelling of the cortical substance of the kidneys, which were much enlarged and, as a whole, anæmic. In the pustules of the skin, in the mouth, and in the parenchyma of the liver and kidneys, streptococci were found.

Histological investigation showed that this eruption, which at first resembled acne, and later, small-pox, owed its origin to the embolisation of the cutaneous vessels and the saturation of the epidermis with streptococci. The resemblance to the variolous eruption was more than external; as yet no form of vesicle has been described so like it as this. Since, in this case, the infectious agent could be demonstrated in the form of relatively large organisms, whose extension exactly corresponded to the degenerated areas, and the variolous structure thus appeared to be the result of a universal coccal metastasis, we see the great importance of this case in the explanation of the genesis of the variolous pustule, which also developes on an infection proceeding from the blood vessels.

Central sections through the larger vesicles show striking appearances. We have before us large, septate cavities, covered with thick horny layer, which are produced, exactly as in small-pox, by the alternate liquefaction and compression of perpendicular, adjacent, epithelial areas, which project in the centre over the level of the skin, or show here a shallow depression, and often a radial, fan-shaped arrangement of cavities and septa, extending from a centre at the base, which is formed by a greatly swollen papilla. These changes, distinct even with a low power, are greatly amplified by the high power, on those sections which are stained for micro-organisms, for the papillary body invariably shows in the centre a dense colony of streptococci, while all the cavities of the phlyctenula above are filled by the same organisms. Wherever liquefied epithelium or necrotic trabeculæ are found, we see these cocci arranged in dense collections, in delicate chains, either radially or coiled. And we can also follow the cocci, on serial sections, into the cutis, first from the connective tissue of one or more central papillæ into its blood capillaries, and from here into the arterial capillaries and arterioles of the central cutis, very rarely to the subcutaneous margin or the small veins of the same region. In the latter segments of the circulation, we find only small marginal colonies or very scattered groups of four to eight cocci, while under the centre, the papillary loops and some of the horizontal arterial branches of the papillary vessels are filled with dense

masses of cocci. Finally we can follow the cocci from these areas into the lymph spaces of the papillæ, and from here into those of the epidermis.

Altogether then we find here the most perfect type of a coccal embolus of the papillary body, and, in direct connection with it, infarction of the epidermis in its lymphatics with the same organisms, while the inflammatory and degenerative appearances produced, repeat the structure of the variola eruption, even to the smallest detail. What every investigator of variola has sought, as yet in vain, we find here in abundance, and must therefore not lose the opportunity of learning, at least by analogy, from the striking morphological identity, as much as possible of the genesis of the variolous pustule. For this, it is naturally especially necessary to study the genesis of these, so remarkably variola-like spots, in order to avoid too hasty conclusions as to the migration of the organisms. But I should first like, in a few words, to indicate certain points of *difference* between this streptococcal phlyctenula and the variola vesicle,

These are neither many nor important. In the fully formed streptococcal vesicle the thickness and slight compression of the covering is striking; it consists of an old upper horny layer, a very much swollen basal horny layer, five to ten times the ordinary thickness, and a broad loosened granular layer, in which the kerato-hyalin is still very well preserved. The swollen basal horny layer consists of rhomboidal cell bodies, with sharp edges and a faintly or still deeply stained nuclear remnant. This strikingly loose formation of the vesicular covering depends on the fact that, at the commencement of the formation of the vesicle, the epithelial œdema attacks the horny layer also, so that for a time the eruption consists of two equally broad layers, an inner one containing the elementary vesicles of the prickle layer, and an outer one composed of swollen transitional and basal horny layers.

Thus the difference depends on the fact that the lateral parts of the vesicle, less directly affected by the poison, show a considerable inter-cellular œdema, while in variola the œdema is mainly cellular, *i.c.* parenchymatous. This is evident even in the initial papular stage. In some places we find, as the first change, simply a great dilatation of the inter-epithelial lymph spaces, along with only slight swelling of the epithelial cells themselves. Further, the spaces above the basal prickle cells (germinal cells) dilate so much, that more or less widespread separation of the prickle layer from the papillary body takes place, only the basal prickle cells remaining adherent. From these super-basal fissures, finer fissures extend further into the prickle layer, and there thus developes, here and there, a net-work of fissures in the

prickle layer, before the prickle cells themselves degenerate. This tendency to a widespread, super-basal formation of fissures, which is found in variola, only in the prickle layers of the hair follicles, is, in this streptogenic pustular disease, of course also found on the hair follicles, and throughout their whole extent, and indeed now and again on the external epithelial wall of the coil glands.

The greater prominence of the inter-cellular œdema has two natural results. On the one hand, even at its acme, the lateral swelling of the epithelial cells is relatively slight, and thus an important factor of the central umbilication is wanting. Consequently it is only exceptionally so developed as in Variola. Then the inter-cellular œdema, in the deeper layers of the prickle layer, leads now and again to the solution of the protoplasm of whole epithelial cells, and thus we have scattered or reticular spaces in the prickle layer. This colliquation of the whole protoplasm of the cell by the lymph differs from "reticulating degeneration," in that the ectoplasm of the cell is liquefied along with the endoplasm.

Otherwise the degenerative products behave, in the mature vesicle, just as in variola. The prickle cells next the granular layers undergo reticular degeneration, and there is often a swelling of the upper layer over the under one, by subsequent œdematous dilatation of the cavities and peripheral extension of the reticular degeneration, analogous to the extension of the upper part of the pock, as the crest. The epithelial cells, lying next the papillary body, swell up as a whole, with amitotic nuclear division, and are most of them transformed into round, loosely connected, multi-nucleated balloons. The main and supplementary trabeculæ, remaining between the primarily swollen and colliquated epithelial cells, consist of compressed nucleated epithelium, which undergoes a slight necrobiosis, and does not importantly differ from the septa of the variolous pustule.

This identity of the main degenerative changes thus identifies the architecture of the mature vesicle with that of variola. The prominence of interstitial œdema in the streptogenic eruption, is certainly more evident by the multiple formation of fissures and spaces in the under parts, and the subsequent great serous distension of the cavities in its upper segment.

Rather remarkably, the peculiar interstitial œdema of Phlyctenosis streptogenes does not extend to the cutis. The circulatory conditions (greatly dilated capillaries, moderately dilated lymph spaces, no large œdematous space) resemble those of Variola and Varicella and not those of Measles. It is, here as elsewhere, clear, that the dilatation of the inter-epithelial lymphatics is not to be explained on simple mechanical grounds; it is limited in this case by the cutis margin, and is therefore

not a result of œdema of the cutis, but a special action of the poisonous lymph.

We find a distinction from the variolous skin, firstly, in a much slighter infiltration with young connective tissue cells, and secondly, in the complete absence of that local leucocytosis, which distinguishes the second period of variolous pustulation. In both points, Phlyctenosis streptogenes rather resembles Varicella than Variola. So far as concerns the stationary cells, we find, only exceptionally, well-formed plasma cells, although, on the perithelium of almost all the capillaries, we find the foundations of their formation laid in greater protoplasmic granulation and rounding of the spindle cells. Mast cells are not especially abundant, but are more frequent and larger than normal. That the emigration of white corpuscles is almost completely absent in the mature distended vesicle, is a very remarkable and instructive fact. It is explained by the fact, that in this case the death of the patient took place before the organisms in the eruption had perished. It points again to the fact, that in Variola the suppuration is probably not produced by the poison itself, but by the chemical substances set free on the death of the germs. The germs of Varicella, again, perish so rapidly that there is only a moderate emigration, before the vesicle dries up.

The epithelial appendages show more marked changes than the cutis in general. The prickle layer of the hair follicles shows frequent liquefaction of individual epithelial cells, and consequently reticular, branched formation of fissures, especially between the external basal cell layers and the inner epithelium. Occasionally, as in Variola, a young hair sheath cylinder, along with the hair, is completely loosened from the hair follicle, to which only remains of the basal epithelial layer adhere; a proceeding quite analogous to the vesicular formation of the surface epithelium. The hair itself is not altered, but the horny layer, which clothes the necks of the follicles, is very much swollen, when these are in relation to the coccal emboli and vesicles. Still more characteristic are the changes of the coil glands. Where these run through the vesicles, the epithelium of the duct is well preserved, even the granular cells at its mouth; but all the cells are very voluminous and partly œdematous. Most swollen, however, are the inmost epithelial cells of the duct, and the cuticular cells beneath. These represent, as we know, the (condensed) cornification of the duct epithelium towards the (inner) surface, and are normally soaked with grease, like the basal horny layer on the surface, into which layer they open. It is consequently not without interest to note that they share the fate of the basal horny layer, and swell up very much. The swelling and increase of volume extends to the cuticular cells of the

whole duct, as far down as the secretory coil glands, and is so great, that the cuticular tube, as a whole, has not room in the duct, *and winds here and there inside it.* Even with the low power one can see this remarkable picture of a winding, internal cylinder inside the coil duct, which is somewhat swollen, especially in its upper segment. In the coil itself we find no swelling of the epithelium, but an inter-cellular œdema, which here and there separates the cells from the glandular membrane, and, now and again, spaces, which have developed from the total colliquation of individual epithelial cells.

As a whole, then, the epithelial appendages show changes analogous to those of the surface epithelium: great swelling of the recently cornified cells and interstitial œdema in the uncornified layers, with complete liquefaction of individual cells, by which the connection of the germinal layer with the rest of the epithelium is loosened.

The explanation of the points of difference between our phlyctænosis and Variola has been already made sufficiently clear in describing the formation of the former, so that we may at once proceed to the consideration of the most important question: *what is the temporal and local relation of the coccal invasion to the development of the vesicle?* It has already been remarked, that the oldest and largest vesicles appear to favour the tempting assumption, that every liquefied epithelial area directly corresponds to a group of cocci, and that the necrosis is the result of the emigration of cocci into the prickle layer. Every cavity, from the margin of the cutis up to the horny layer, is filled with cocci, in rows and spheres. But this assumption is contradicted, step by step, the more we examine earlier stages of development, and I will at once state the ultimate result of these comparative studies. *It is this: all the epithelial changes, up to necrosis of the epithelium, are the results of the action of a poison dissolved in the serum, and are already developed when the emigration of cocci from the cutis into the epithelium begins.*

In relation to the distribution of the cocci, we can distinguish three stages of the process. The smallest, mustard-seed vesicles show, in the epidermis, the papular stage, the prickle layer, permeated by wide lymph spaces, showing in its under part reticular spaces from the complete liquefaction of some epithelia, others of which are partly dissolved and deprived of the greater part of their protoplasm, but not of their nucleus; in its upper part the commencement of reticular cavity formation, and as a cover the œdematous swollen granular layer and basal horny layer, apparently supported by columns of non-liquefied but compressed epithelial cords and uninjured sweat pores. At this stage no cocci can be found in the vesicle, but a dense colony of streptococci always occupies exactly the centre of the papillary body beneath, forming infarctions in one or more capillaries, and extending, with

diminishing density, into the neighbouring arterioles. Indeed I find the extension of the cocci in the vascular system at this early stage often more distinct than in the succeeding stages.

We may describe the transformation of the papule into a vesicle, as the second stage. It then becomes about the size of a split pea, at most two millimetres over the level of the skin, and often shows a slight dimple; the spots often run together to form patches of vesicles. The irregular changes, which the inter-cellular œdema induces in the under part of the prickle layer, diminish, the more individual epithelial cells and collections of them are detached, and undergo ballooning degeneration, with amitotic nuclear increase. The upper part of the vesicle is also greatly distended by advancing reticular degeneration and the running together of developed cavities, which are filled with finely granular, coagulated lymph, without the reaction of fibrin, and assumes a regular form and homogeneous appearance; the vesicle is mature. Underneath it, the cocci have extended their wanderings, they have passed from the capillaries of the papillary body into the lymph spaces, and from there into the widely open lymph spaces which communicate with cavities of the lower prickle layer. Rather remarkably, the immigration into the epithelium does not take place, chiefly, in the centre, where the growth of the cocci is greatest in the cutis, but laterally, at the periphery of the eruption. Possibly the soil here, where many more unaltered epithelial cells are present, is better. Both the delayed immigration of the cocci into the vesicle and the selection of other than the immediately adjacent epithelial areas, show that other than mechanical causes determine the distribution of the organisms in the tissue.

At the acme of vesiculation, we still find the cocci in the cutis unchanged, or more sparing deep down, and, in the vesicle, only in quantity at the œdematous base of the periphery. A few chains extend from here, especially along the coarse trabeculæ, into the vesicle, but these are few in many mature vesicles, and often altogether absent.

The third stage of the eruption may be considered as that which is macroscopically evident by the increased contents. The circumference is not much changed, but the height is now about three millimetres, and the dimple is usually flattened out. Nothing is altered in the formation of the vesicle, except that the reticularly-degenerated parts of the upper prickle layer are still further distended by coagulated exudation, and the cover and lateral walls of the vesicle are more compressed. But the cocci are found in luxuriant, pure cultivation, on the dead soil in all the spaces of the vesicle, and permeate the exudation which fills the cavities. Here we see the most delicate and

the longest chains, while, in the narrower spaces of the blood capillaries and in the super-basal fissures, the cocci form dense collections, and do not so distinctly show their streptococcal character.

In distinction to the positive occurrence of numbers of cocci, a negative one is of importance, that is the absence of invasion of the coil glands. There is a tendency to attribute the presence of bacteria in the sweat to their having come through the coil glands, and conclusions have frequently been drawn, not histologically, but solely from the presence of the organisms in the sweat of the skin, regarding their penetration of the coil glands and their separation by them. It is not necessary here to enter on the fallibility of this conclusion; but we must point out, that in this case, where streptococci have not only circulated in the blood, but formed extensive infarctions in the capillaries of the skin, from which they wander into the epithelium of the surface, the coil glands are absolutely free. Their epithelium and that of the ducts show, as already indicated, swelling and liquefaction, like the epithelium of the surface, indeed, one often finds in the capillaries, which run along the coil ducts and the coils, dense obstructive masses, without the cocci anywhere penetrating into the structures. Apparently the mechanical conditions are the most favourable conceivable, the epithelial soil is prepared in the same way as the surface epithelium, and yet there is no question of a penetration into the coils, to say nothing of an excretion by them. The selection of the cocci is different in every medium, and cannot be determined offhand. But even if one were to find in similar cases that a few cocci had penetrated, and did not at the same time observe them in the sweat pore, the fact of a separation by the coil glands would by no means be established.

The distribution of the streptococci and their action on the cutaneous tissue may be summed up in the following conclusions:—

1. The formation of œdematous and necrotic areas in the epidermis is a remote action of the growth of the cocci in the capillaries of the skin.

2. The necrobiotic regions of the epidermis have not developed from the invasion of the cocci into the epidermis itself, but form a suitable soil for them, which they occupy on a principle of selection, and not simply mechanically.

3. However great the collection of streptococci in the epidermis, there is no necessary suppuration in the skin.

4. Complete obliteration of the superficial capillaries of the skin with cocci does not necessarily induce hæmorrhage.

5. However favourable the conditions of growth for the streptococci in the skin, the extension to the coil glands is not a necessary result.

These propositions may be of use in the investigation and estimation of the true organisms of Variola, Varicella, Zoster, and similar epidermic diseases.

Pustulosis Staphylogenes.

The investigation of the following case, which forms the subject of Deutsch's dissertation (On Cryptogenic sepsis, Heidelberg), I owe to the kindness of the Right Hon. Dr Arnold and Dr Ernst. The histology of the cutaneous affection in this case is found briefly in the above dissertation, and I am able to confirm, and in some ways to amplify the observations of the author.

Margaret H., 16 years old, was attacked with sacral pain and rigor, with the appearances of acute articular rheumatism. An affection of the meninges and lungs developed, and the patient died ten days after the commencement of the disease. Two days before death there appeared, here and there on the breast and upper extremities, more numerously on the abdomen and legs, an eruption, which consisted of bluish-red lenticular spots, disappearing on pressure. On the next day there appeared, on the same places, numerous pin-head vesicles, filled with watery contents, sometimes on hæmorrhagic bases. From such a spot a small quantity of watery-blood was taken and inoculated on agar ; it gave a pure cultivation of staphylococcus pyogenes aureus.

Post-mortem : Purulent myocarditis, multiple miliary abscesses in the lungs, kidneys, liver, intestines ; abscesses in the right psoas ; purulent periostitis on the sacrum and in the lumbar vertebræ. In the centre of miliary abscesses the same cocci were everywhere found in zoogloœa form. In the vessels there were numerous cocci, sometimes as embolic plugs, sometimes free in the lumen. There was a distinct connection between the coccal emboli and the hæmorrhages and miliary abscesses of all the organs.

The contents of the pustule consisted of a fluid detritus and cocci. At its base a dense collection of round cells, with a central colony of cocci, evidently formed the centre of the eruption ; only those capillaries immediately under it were stuffed with blood, and they alone contained cocci, so that the whole process gave the impression of coccal emboli of the cutaneous capillaries, as in other pyæmic metastases.

In the examination of this case, my attention was mainly directed to the following two objects : First, to establish the difference between these true embolic, pustular diseases and the *staphlyogenic impetigo* from without, and then to determine the points of resemblance and the distinctions between it and the *streptogenic phlyctænosis*, which has just been intentionally so thoroughly described, and which I venture to establish as the type of all embolic epidermic diseases.

The different pustules in my possession all show the same form. Even with a low power it is very clear, as Deutsch notes, that all the capillaries underneath the pustule are dilated to a maximum, and gorged

with blood; this dilatation extends a little beyond the epidermic affection. Then, from the capillaries lying beneath the centre of the pustule, emigration of leucocytes takes place, and the surface of the cutis, along with a thin layer of surface epithelium, which forms the base of the pustule, is densely beset with them. These two symptoms suffice to distinguish the embolic pustule from impetigo; they indicate, with the greatest clearness, the severe injury of the vascular connective tissue in the former.

On the other hand, there is absent in pustulosis the characteristic occurrence of cocci in the roof of the pustule and the follicles which run through it. Even if the cocci have here reached the horny layer, there is still no question of a penetration, to say nothing of a permeation of the horny layer with cocci, such as is so frequent in impetigo.

And the extension of the cocci inside the tissue is characteristically different in the two affections. In the most recent impetigines they are only found under the horny layer in the centre; from here they grow, separating the horny layer from the prickle layer, peripherally in all directions, and then radially into the drop of pus, without reaching the epithelial margin. In pustulosis they are also found in great collections under the horny layer, but at the same time they diffusely permeate the whole pustule, and form everywhere, even on the base of the pustule and in the swollen papillary body underneath, large, rounded, irregular areas. Since we know from the history that the eruptions did not appear as pustules but as watery vesicles, all my sections must represent the later stage. The leucocytosis has developed secondarily, one day after the appearance of the vesicle, and one day before death. In view of this rapid growth of the cocci, and their spread, wide though it be, on and in the base of the pustule, and in the cutis, it is not possible that they can have grown in this short time so far downwards beyond the ordinary borders; they must have extended from below outwards, and on a soil already prepared for such a rapid extension.

A last point in favour of this is the presence of the cocci in the dilated capillaries themselves. They are certainly only found singly as diplococci or at most in groups of fours, never as zoogloœa balls, as in the lymph spaces. But their presence in the blood vessels of the pustular base in impetigo is altogether unknown.

In addition to these coarse differences, there are certain finer ones, which are important in connection with the others. While in impetigo the prickle layer is mechanically depressed by the drop of pus, without showing any injury to the epithelial cells, it is in pustulosis much degenerated. In some pustules the papillæ lie quite free, in others covered with a few layers of prickle cells, permeated by leucocytes;

the remainder of the prickle layer lies partly loosened on the covering of the pustule, and partly free in the pus, in the form of smaller or larger balls. All the detached parts of the prickle layer are difficult to stain, even their nuclei are hardly recognisable. Some of the epithelial remains, hanging from the pustular covering, are compressed into trabeculæ, and recall the torn septa of a variolous pustule. But all the pustules are strictly monolocular. The lateral limitations of the pustule also recall the variolous process, for the prickle cells—though in very different extent and severity—are drawn out into bands, which are stained with difficulty, or are also swollen, and then form small peripheral pustules. Further, the poisonous action is shown, in the epidermis surrounding the pustule, by a swelling of the upper, older layers of prickle cells, exactly corresponding to the capillary dilatation.

From these facts we may draw the probable conclusions: that the primary vesicular stage of the process shows a swelling and necrosis of the older prickle cells, and that the vesicle forms inside the upper half of the prickle layer, and leads to more or less widespread necrosis of the whole prickle layer, thus differing as much from Impetigo as it resembles streptogenic phlyctænosis. With this latter, pustulosis has also in common, the swelling of the papillary body underneath the pustule, and its partial deprivation of epithelium.

But, on the other hand, there are striking differences between these two embolic eruptions. Leucocytic immigration is completely absent in streptogenic phlyctænosis, and the distension of the blood capillaries is much less evident. Then their structure is much more varioloid, on account of the segmentation of the vesicles.

Finally, the cocci in it are also found in obstructive balls, in the capillaries of the base of the vesicle itself, while in pustulosis, in spite of much greater vascular paralysis, only single cocci are found.

The streptococci are evidently much better adapted to growth in the circulation, and have much less leucotactic action than the staphylococci.

It is very remarkable that the staphylococci not only induce a vascular paralysis by their presence in the vessels themselves, but a wide-spread necrosis of the epidermis over them, while, when they penetrate under the horny layer, the much nearer prickle cells show no signs of necrosis. And it is equally striking, that, while in the latter mode the attraction of leucocytes is the primary symptom, in their remote action from the vessels the leucocytosis first appears secondarily, after the necrosis. This display of new properties, in their action from the circulation, is capable of different explanations, whose value can only be decided by further experience. Either we are dealing, in spite of the microscopical and cultural resemblances, with

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another organism, or with the same organism with altered toxic properties, or thirdly, the immigration of staphylococci is, in Pustulosis as in Variola, a secondary infection; we are dealing with a mixed infection, of which the original one is as yet unknown. There is much in favour of this latter hypothesis, according to which capillary dilatation and epithelial necrosis—in short, everything which is not proper to the staphylococci—would be ascribed to the primary organism, while the staphylococci would only later take possession of the injured area of skin. This would do away with the difficulty, that the centre of leucocytic attraction is seated in the epithelium, for the staphylococci, if they alone induce the changes, ought to form such a centre in the vascular connective tissue. It would explain why this embolic Pustulosis staphylogenes is so extremely rare, while Sepsis staphylogenes, with or without Impetigo staphylogenes, is by no means infrequent; the embolisation of the skin with staphylococci is prevented, if some particular condition, *e.g.*, primary embolic necrosis of the skin, is not present.

At all events this embolic pustular disease, of the nature of an acute eruption, caused by staphylococci, is, in distinction to the externally inoculated staphylogenic impetigo, an excessively rare affection of the skin, and in its assumption during life one must not only be very cautious, but always search for a mixed infection.

Section III.

PROGRESSIVE DISTURBANCES OF NUTRITION.

A. Malignant new formations.

Carcinoma.

The very multiform histology of cutaneous cancer is not represented by an equal multiformity of the clinical appearances. Most cases commence so stealthily, that we have nothing but the statements of the patients to go on. And these teach us little more than that, sometimes a fissured, warty protuberance, sometimes a smooth nodule, a seborrhœic crust, a simple, irritated wound or erosion, or a mother's mark previously existed at the seat of the cancer. Only where the carcinoma forms the last stage of some well-known dermatosis, and developes from it necessarily (Xeroderma pigmentosum, Sailor's skin, chimney-sweep's skin, paraffin skin, Leucoplacia, Jacob's ulcer, Paget's eczema) or exceptionally (Lupus, Syphilis, Mycosis fungoides, Ulcus cruris) is the genesis of the cancer more evident, and in some of these cases the histological form of the cancer may be prophesied from the previous clinical condition. In other carcinomata we are only very exceptionally in a position to do this, namely, in those which, by particular phenomena, demonstrate their character on the surface, like the papillary, villous, or those cancers which are covered with expressible epithelial plugs. We must therefore consider most forms of cancer of the skin, at present, under the common name of Carcinoma vulgare, leaving it to the future to separate certain clinical forms, and to prove their distinct histological characters. I shall therefore group together under Carcinoma vulgare, without particular regard to the clinical condition, all varieties of carcinoma, which do not form the last stage of a definite skin disease, and endeavour to class them solely on an anatomical basis.

Then I shall devote some space to the few varieties of carcinoma, whose previous history is known (Xeroderma pigmentosum, sailor's skin, etc.), as an earnest of a future, more exact analysis of cancer, in which the deduction of the histological characters from the clinical appearances will be attempted.

1. *Carcinoma vulgare.*

The old division of carcinomata of the skin into "flat" and "infiltrating" was not made by Thiersch; it appeared at least ten years before, in the works of Hannover (1852) and Paget (1855); but the epoch-making work of Thiersch (Ueber den Epithelial Krebs, namentlich der Haut, 1865) first brought it into general notice, and even yet that work is very largely quoted. With the amplitude of clinical and histological facts, which hardly admit so simple an arrangement of the cancers, its tenacious retention by authors is difficult to understand, but it makes it necessary for us, since certain, often misunderstood points in the question of cancer are supported on this division,* to consider it somewhat particularly. In the magnificent work of Thiersch, this very point is the least clear and convincing. At first it appears as if, as the nomenclature signifies, the topographical arrangement sufficiently distinguished "flat" and "infiltrating" skin cancers. The "flat" cancer is, according to Thiersch, a superficial epithelial new growth, a few millimetres thick, which on section is pretty well marked off from the stroma (p. 51). The "infiltrating cancer," on the contrary, has an ill-defined margin, and extends irregularly into the deeper tissues. But a few pages later Thiersch censures Paget's expression, "superficial cancer," saying that "this may give support to the erroneous idea that the disease may *remain* superficial, that its action and effect are superficial, and not, as is the case, destructive of all lying beneath it, and thus penetrating deeply" (p. 53). But when Thiersch rightly recognises every cancer as gradually attacking the deeper parts, he shows his own division of "infiltrating" cancers to be as little correct as Paget's group of "superficial" cancers, and the whole criterion of superficial or deep position, as a principle of division, to be insufficient.

Another remark of the author concerning the natural grouping of the epithelial structures leads next to search for the true difference between these forms of carcinoma, *in their more superficial or deeper lying points of origin.* On the one hand, according to Thiersch, the hairs of the beard (lip and chin), the sweat glands and the sebaceous glands of the beard hairs form the "infiltrating group," and the epidermis, the lanugo hairs and their sebaceous glands, the "superficial group" of the epithelial structures (p. 101). And, indeed, he founds on this the proposition: "the flat form of epithelial cancer usually developes in the Malpighian layer and the lanugo glands." But the study of his cases and his beautiful diagrams show the untenability of this criterion, for a number of "infiltrating" cancers take their origin

* Compare Ulcus rodens.

from the prickle layer, while the sweat gland cancer is indicated as "flat." And so the hopes of the reader are finally reduced to looking for the salient point of Thiersch's division, *in the form and development of the cells.* In several places in the book the author refers to the difference between his groups in this respect:—"While in flat cancer the epithelial development does not go further than that of germinal and indifferent cells, since the cells, before they have attained a definite individual stamp, become loosened and liquefied, we see in the case before us (an 'infiltrating' cancer) the cells being transformed into flat, flakey structures, and retaining their individuality under many changes" (p. 126). Thiersch here indicates the well-known degeneration of those cancers, which undergo central liquefaction, in contrast to those forming the concentric layers, which we know as epithelial and horny pearls (cell nests). The former cancers, which—as Thiersch says—follow the gland type, are the "flat"; those forming epithelial and horny pearls belong to the "infiltrating" form! The reader of the present day might well prefer to believe the opposite. Indeed, present-day experience in no way favours the view just given. Of seventy cancers of the skin, which I have examined, there were four pure, horny pearl cancers, which were, clinically, pretty flat cancers of the lip, a few millimetres deep, and yet, histologically, all of them arose from the surface epithelium, and there were eleven cancers undergoing central liquefaction, which, on account of their irregular extension in the deeper tissues, would have to be reckoned with Thiersch's "infiltrating" group; one of them for the further reason that it took its origin in the coil glands.

Neither the actual extension in the skin, the point of origin, nor the ultimate fate of the epithelial cells entitle us to-day to regard the division into "flat" and "infiltrating" (Thiersch) or "superficial" and "deep" (Paget) cancer as correct. Every cancer, which becomes malignant, metastatises, and leads to cachexia, is "infiltrating," and every cancer (even the glandular cancers of the skin), has, on the other hand, a benign, purely local stage, in which it is more or less "superficial" or "flat." On these terms, no practically useful division of the forms of carcinoma can be founded. But the distinction is more than superfluous, it is dangerous, for—at least in Germany—it has, up to now, even for the best observers, obscured the peculiar nature of certain cancers, which differ from carcinomata, and for which the epithet "flat" or "superficial" has actually some application (Jacob's Rodent ulcer).

By simply excluding, in his group of "flat" skin cancer, the Rodent ulcer of Jacob and his English followers (p. 31) (in his 102 cases there were no rodent ulcers), Thiersch has only made more

difficult for his successors the important distinction of that quite peculiar variety of flat cancers from other carcinomata. In many places where investigators are familiar (as in England) with Rodent ulcer, but not in the same degree with the work of Thiersch, it is commonly understood that German surgeons understand by "flat skin cancer," the true Rodent ulcer, which is by no means the case, for only few of them know it. On account of this prolonged confusion, it is probably not advisable to restrict, for the future, the name of "flat skin cancer" even to Rodent ulcer, although it has most right to the name; the definitions "flat" and "infiltrating" must be discarded.

Another promising plan is, to divide the cancers of the skin, according to their histologically apparent points of origin, into those of the surface epithelium, the follicles, and the sebaceous and coil glands. The idea is so far good, for new growths in their further development retain certain peculiarities of their primary arrangement, much in the same way as any peculiarly formed cells of a primary carcinoma (*e.g.*, cylinder cells), are found again in its metastases. Accepting this view, one is easily induced to ascribe carcinomata of the skin with hollow cylinders to the sweat glands, and those arranged in acini to the sebaceous glands. Admitting that a more thorough histological analysis were to confirm this hypothesis, a practical division cannot very well be founded on it, for such peculiarly formed new formations are, in the first place, very rare, and would therefore form only a small appendix to the great mass of ordinary cancers; and secondly, such a division has no direct relationship to our clinical knowledge of cancer. We cannot recognise, macroscopically, these differences of development of cancers of the skin from different areas of epithelium, and we cannot correlate their clinical appearance and their anatomy.

But histological examination by no means confirms this view. The majority of skin cancers shows us, that the prickle layers of the epidermis and the follicle have exactly the same relation to the development of epithelial buds; the cases are rare where only the one or the other region of prickle cells is exclusively concerned, and the one set differ in their other characters, in the cell forms, &c., so little from the others, that carcinomata of the surface and follicle epithelium must certainly be treated together. The question regarding the sebaceous and coil glands, is more difficult.

So far as concerns the sebaceous glands, Thiersch is inclined to ascribe to them an important rôle in the origin of carcinomata. His grounds for this are chiefly of a topographic nature; the nests of cancer lie near the place where the sebaceous glands ought to be, and these are absent, while the hair follicles are still present. These criteria are by no means sufficient in themselves for the identification

of sebaceous gland cancers. The sebaceous gland itself is a structure too little persistent to resist any irritant of a formative nature. Just as simply as the transformation into a fatty secretion takes place, so simply does the gland retrograde, rapidly, into a purely epithelial projection, which only gives a hint of its origin when it encloses a circular mass of fat, or a few sebaceous cells.

There is scarcely a carcinomatous growth of the follicular epithelium, in which the sebaceous gland beside it does not disappear, without having given origin to any kind of growth. Not the absence of the glands, with the presence of the carcinomatous growth, but only their remains inside the growth, entitle us to conclude that a cancer has arisen from them. And this, in cancers of the lips and cheeks, so far as they arise in regions with strong hairs and small sebaceous glands, is hardly ever seen.

It is otherwise with cancers which arise in regions (nose, back, forehead) which have large sebaceous glands with small lanugo hairs. Here one indeed usually finds—thus satisfying the postulate—sebaceous cells and sebaceous secretion, enclosed here and there in the cancer masses. And how could it be otherwise, where almost all the epithelium of the deeper parts is represented by the epithelium of the sebaceous glands? But these cancers further betray themselves by an acinous formation, certainly incomplete, but still recognisable, and so it is very probable that this arrangement has some sort of connection with the acinous type of the sebaceous gland. Certainly, however, these radially arranged, knobbed (acinous) cancer nests contain only very seldom these sebaceous cells, and then, putting aside the acinous type, every suggestion of the origin from the sebaceous glands disappears. One must therefore never expect sebaceous gland-like cancer nests as one finds mammary gland-like ones in certain cancers of the breast. When one further finds other cancers of the same region, in which the origin of the tumour from the surface epithelium is quite evident, and where nevertheless the same acinous type is present, without any relation to the follicle, the significance of the sebaceous gland type, as a standard for skin cancers, must be relegated to its proper place.

We have, beyond doubt, to do with them in a small number of cancers, which take their origin from undegenerated sebaceous gland epithelium, as from other cutaneous epithelium at the same time. But the sebaceous gland structure is always immediately lost in the growth, and the acinous-like type, which later suggests sebaceous glands, is shared by other carcinomata of the same regions, which do not arise from the sebaceous glands. We must therefore conclude that the region, as such, predisposes to a particular type; it may be that the

epithelium (surface or follicle epithelium) or the structure of the connective tissue has a definite influence in this direction. We can only admit a *pure sebaceous gland cancer*, where this evidently proceeds from the sebaceous glands, and not at the same time from the epithelium of the surface, the follicles, or the coil gland (case 37 of my collection).

The same is true of the much rarer cases of coil gland cancer; there are such, Thiersch described a genuine one. They are, from their peculiar position and characteristic epithelium, more easily referred to their point of origin, and recognised as actual coil gland cancers. But here also the coil character of the new growth disappears immediately with the cancerous development. Here and there a tubular development of the cancer still recalls the tube-like structure of the coil gland, but it is not general, and in some cases is absent. And thus the type of coil gland cancers is by no means always the same; the point of origin is not able to stamp the complete new growth with a uniform and characteristic appearance.

And so this method of analysis does not lead us to any useful plan, by which we may be guided through the extraordinary number of variations of skin cancer. But if the original type of epithelial cells leads us to no striking differences, we may perhaps find them in the different developments of the epithelial growth. As a fact, the appearances which are supplied by the centrally liquefying, the cornifying, and the calcifying carcinomata, are characteristic enough. These degenerative or retrogressive results are not limited to epithelium, either of any special origin or special localisation. They are, in any particular case, usually applicable to all its parts, and so possibly in the future there may be discovered definite, important relations between these degenerations of carcinomatous new growths and the still unknown etiological factors. But at present these are hidden from us, and since the degenerations appear only in some of the cases, these later changes in the new growths have for us only a secondary interest.

After these explanations we now come finally to that factor which appears to me to satisfactorily reduce the majority of skin cancers to a few types. This I find in the gross histological appearance, in the *architecture of the carcinomata.*

But it is not only that practical result, which in my eyes justifies the following classification, but especially the consideration that this architecture, that is the disposition of epithelium and connective tissue, of cancerous tissue and stroma, is definitely settled by the relationship of each to one another. Thus the classification at once introduces, in every case, the appearance of the "strife of the embryonic layers," their weakness and strength in each case, and the types thus attained correspond to well-known appearances, which may be, both clinically

and prognostically, separated. And such a harmony is ever the best test of a scientific arbitrary arrangement.

I recognise three chief forms and a sub-form of cancer of the skin. The chief forms are: 1. the *Fungating*; 2. the *Cylindrical*; and 3. the *Alvcolar.* These have in common, that they ignore the natural structure of the skin, for the advancing epithelium strikes out new paths. Opposed to them stands a fourth form, which uses the already present lymph channels, without undermining the whole structure of the skin, the form of *Carcinomatous lymphatic Infarction.* But this is only a sub-form, and is only present in cancer secondarily affecting the skin, and in metastases (Waldeyer).

The **fungating cancers** are those which proliferate most luxuriantly, and therefore very rapidly affect their surroundings, appear in the neighbouring lymph glands, and give origin to metastases. Histologically, this character is expressed in the widespread and equal distribution of epithelial mitoses. The epithelium has, in its growth, become quite independent of the vascular connective tissue, and it swells up into large clumps, which grow through the connective tissue in the most irregular fashion, and frequently run together, so that the stroma is almost reduced to the vessels and their immediate surroundings. This form of cancer is not so frequent on the skin as in other, softer organs; of my seventy cases of skin cancer, only seventeen belong to it. Clinically, the extreme epithelial proliferation shows itself in the nodular and tuberous swelling of the skin.

In this group we may distinguish two sub-varieties, which, although externally and clinically very different, still spring from the same principle of growth: 1, the *villous* and *papillary*; 2, the *coarsely reticular.* The first, the so-called papillary or "*zotten krebs,*" has previously been ascribed to a mysterious tendency of growth in the papillæ, which—as a complication of the proper cancerous growth—was characteristic of certain cancers. Even Thiersch, in his pioneer work, takes this view of papillary carcinomata, although he himself, in discussing a villous cancer of the back of the hand, supplies a weighty argument against the view, by drawing attention to the fact that the papillary character is present, not only at the borders of the ulcer, but also on its surface, where the papillary body had long been destroyed. It is well known that, since his time, Auspitz and his followers, in the question of the papillæ, have supported that which Thiersch and Waldeyer did in the cancer question, namely, the recognition of the *definite influence of the epithelial growth* on the form of this structure. But, since then, the papillary cancer is no longer recognised as the complication (combination) of carcinoma with an "ad hoc" assumed "papilloma," but—like the normal papillary body—as the simple wavy or even dendritic furrow-

ing of the stroma by the growing epithelium. Since the more thorough observation of the mechanism of this process has already proved this view to be the only correct one for most papillary structures of the skin, we are to-day no longer compelled to limit ourselves to this mathematical motive. We possess, in the recognition of mitosis in the epithelium, as well as in the connective tissue, an indisputable basis for the determination of the seat and direction of the tendency of growth, and can require that anyone who to-day speaks of an active growth of the papillæ into the epithelium, shall also prove that this takes place by means of a collection of young cells giving evidence of mitosis. Such a proof is supplied normally by the hair papilla, although here most investigators had already admitted an active growth of the connective tissue into the epithelial germ. Pathologically, this process can only rarely be recognised in the skin, it is almost always secondary, and, compared to the active processes of the epithelium, scarcely needs to be taken into consideration. Under these circumstances it is no wonder that, in the carcinomata, which chiefly consist of new-formed epithelium, the production of the papillary surface is to be attributed to the latter only. And the thorough study of successive cases confirms this view in every connection.

The papillary cancers notoriously develope, preferentially, on the glans penis, then on the hands, feet, and legs, the face, especially the cheeks, the forehead, and temples ; they are rare on the trunk. There is always present in them a sort of misrelation between the very luxuriant epithelial growth and the possibility that the new growth extends, to a corresponding degree, into the deeper tissue. On the glans this is supplied by the close fixation of the thin skin and the resistance of the fascia of the penis, on the hand, face, and leg, by the surfaces of the bones, which are found close under the thin skin. On account of the very luxuriance of the acanthosis, the initial delay of the affection of the deeper parts is usually only of short duration, and after overcoming this resistance the epithelial processes extend all the more rapidly in the underlying organs (corpus cavernosum, bones). And thus the infiltrating form of the fungating cancer is added later to the papillary, and the former is, in spite of its apparently superficial character, rightly dreaded.

The infiltrating form of the unlimited, fungating cancer may be indicated as the coarsely reticular, on the one hand, in regard to the frequent running together of the epithelial processes, which is in this form the rule, and on the other, to distinguish it from the simple reticular form, which is ruled by another law of growth. (See below.)

The cancerous processes are much more multiform in their arrangements, in those forms which are accompanied by a limitation of the

epithelial growth to those surfaces, in contact with the vascular connective tissue; in the **cylindrical type of cancer.** Most cases of skin cancer (36 of my cases) follow, in general, this type; it corresponds most closely to the relations, normally present in the skin, between epithelium and connective tissue.

In this large group, four sub-types may be distinguished :—(*a*) the *reticular ;* (*b*) the *simple cylindrical ;* (*c*) the *acinous ;* (*d*) the *styloid.*

The *simple cylindrical* form (7 cases) most nearly corresponds to the normal epithelial growth on the skin ; it is a simple extension of the normal system of epithelial ridges. Normally, the mitoses are limited to the epithelial layers next to the connective tissue, and the margin between the two layers is much more definitely marked than it usually is in cancer. The form of the epithelial processes, as soon as they overstep the boundary of the normal system of ridges, becomes purely cylindrical. We are here quite right in speaking of epithelial taps,* a word, which, in many pathological illustrations, is used in a way as little correct as it was, until very recently, in normal anatomy. Most carcinomata of the lip provide good examples of this form of cancer. It is not clearly defined from that which I have indicated as much more frequent, the *reticular* form. This (17 cases) developes from the former, by the running together of the epithelial cylinders, and an irregular epithelial net is formed, running through the skin. The reticular form is favoured, on the one hand, by the tendency to free budding of the epithelial cylinders ; on the other, by a less sharp definition from the connective tissue; both forms are etiologically related. But this simple reticular form is always distinguished from the coarse reticular, fungating one, by—in addition to the finer and more evenly thick processes—the sharper development of a boundary zone between it and the connective tissue, and the distribution of mitoses related to this ; the imperfect marginal definition, which characterises the cancers of the first group, is absent.

A very characteristic picture is presented by the *acinous* (4 cases) development of cylindrical cancers. Here also the type is supplied by cylindrical, epithelial processes, which penetrate the cutis in all directions. But the active growth is concentrated on the knob-like, swollen ends of the finger-like processes, and consequently these send off, in different directions, new sprouts, which often—like the acini of a lobule of a gland—group themselves around a centre. Thus there results the acinous character of the new growth. The sharpness of the limitation from the connective tissue contributes its share in making the structure look adenomatous, and only the examination of many sections, which everywhere show transitions into a quite irregular,

* Epithelzapfen.

cylindrical type, as well as certain appearances of reaction of the connective tissue, to which we shall refer directly, place the true malignant character of the new growth beyond all doubt. As noted above, this form is most frequent on the nose, the cheeks and the forehead.

The cylindrical type undergoes quite an opposite development, in the *styloid* form (8 cases). Here the active growth ceases at the ends of the epithelial processes, and they become pointed.

The same takes place on their sprouts, and thus the epithelial part acquires a gnawed, frayed appearance, and soon terminates in numerous pointed processes. The pencil-like pointing of all less active epithelial parts leads to many cancer masses becoming free in the tissue, and others, not completely snared off, are only connected with the neighbouring epithelial masses by very thin bridges.

The *styloid* transformation of the epithelial processes is a result of a powerful resistance of the connective tissue stroma to the invasion of the epithelium, and therefore the expression of a *relative benignancy* of the new growth. It is therefore almost characteristic of the most benign form of skin cancer, the Rodent ulcer of Jacob. But it is not limited to this clinical form, for naturally it often shows transitions to the other forms of cylindrical type, and is often combined with them. But wherever this pencil-like pointing appears, it is a sign, that at that place the new formation has, for a time, ceased, and the connective tissue encapsulation has obtained the mastery.

The third main type of cancer of the skin I describe as the **alveolar.** This may appear remarkable, since we are accustomed to ascribe to all cancers a more or less defined alveolar structure. But this view, which dates from the time of scraped and brushed preparations, proves in the present period of serial sections to be no longer tenable, regarding cancers of the skin. Alveoli, in the strictest sense of the word, that is, distinct, isolated masses of cancer, as the fundamental type of the tumour, we find only seldom. Certainly we can, in most forms, recognise certain snared-off epithelial areas, such as we have noted as the rule in the styloid form. But in such cases we have exactly the opposite of an active growth. And where, in the previously described forms, we see numerous isolated, carcinomatous alveoli in any one section, we will find, with certainty, on the next sections, the connection of these parts with others surrounding, and thus a proof of an actual coil or net-formed arrangement of the epithelium.

But there is a series of cancers of the skin, whose law of growth actually leads to the development of true alveoli, and these alone we will indicate with the old name of "alveolar" (13 cases). In contrast to the boundless, widespread growth of the fungating, and the peri-

pheral growth of the cylindrical form, more limited by connective tissue, the growth here is absolutely *irregular, and extends from many scattered points of the new growth.* But how come these scattered epithelial masses in this place, since the point of origin of epithelial growth is always the same? These, by no means frequent cases, must, at the first glance, *appear enigmatical* in regard to the epithelial theory of cancer, and it was possibly such appearances which led many investigators to the heretical theories of an epithelial infection and transformation of the connective tissue cells. A special tendency of the connective tissue to secondarily snare off the epithelial processes, and in this way to form, on all sides, isolated cancer masses, one can hardly assume in these cases, for neither the richness in cells nor the collagenous new formation in the stroma tends to be particularly well developed; these conditions are only seen in the styloid form. I see no other possibility of explanation than that, in these cases, the *automatic movement* of the cancer cells, which was first seen by Waldeyer, is particularly vigorous. As a fact, it is characteristic of the alveolar carcinomata that, on the border of the new growth, there is always a series of single epithelial cells, scattered like seed. From this to small, round, enclosed nests, and to the largest isolated alveoli, there are seen all the transitions that could be wished for. While, therefore, in those forms of cancer considered above, the advance of the epithelium is, so to speak, caused by the whole new growth, in that every mitotic increase in the centre must tend to push on the peripheral processes in direct connection with it, here, certain individual epithelial cells detach themselves at the periphery, in order to found a nest of cells of their own, which increases the cancerous node, without being mechanically dependent on it. Where this sowing of single epithelial cells goes on unopposed, we get an enormous number of small alveoli—*the small alveolar form;* where it stops for a time, there are developed large alveoli, which are usually surrounded by small nests—*the large alveolar form.* Both have, macroscopically, in common, the light, medullary appearance, and microscopically, the great richness in epithelium. In this relation they may be compared with the fungating cancers of the skin. But while, there, the firmly adherent epithelium only folds the connective tissue into grooves, so that the single areas of connective tissue still include blood vessels, and always have the same relation to the cancer nests as the normal cutis has to the epidermis, we see here an intimate mixing up of epithelial nests and single collagenous bundles, and at many places the swelling of the epithelial nests leads to a rarefaction of the stroma, at least in the centre of the tumour. Since, in the alveolar cancers, the single nests are isolated, they—in contrast to the masses of fungating cancer—

frequently fall completely out of fine sections, and the perforated stroma which remains exquisitely shows the "alveolar" formation.

The occurrence, although rare, of this true alveolar form is of particular importance in two directions. On running through a small series of the most common cancers of the skin, *e.g.*, those of the lip, we might readily come to the conclusion, that the proper alveolar formation did not occur on the skin, that the skin cancers were consequently peculiar. In view of what has been said, we must however admit that a true snaring off of the epithelium does indeed take place, in the same way as in cancer of the internal organs, but that a preference of the epithelium for advancing in closed alveoli is not recognisable on the skin.

And, on the other hand, it is evident, from these facts, that it is impossible to make the diagnosis of cancer dependent on the presence of snared off epithelial areas (Klebs). Many true carcinomata of the skin would not fulfil this postulate. There must be in the cancers of the skin a peculiar principle of growth, probably a peculiar mobility of the cancer cells, which leads to a true alveolar formation.

The sub-form of the *carcinomatous lymphatic infarction* (4 cases) approaches, in certain relations, very close to the alveolar cancers, in so far as we find, here also, a chain of out-posts of cancer cells, and the earlier nests often resemble small cancerous alveoli. But while there, a special property of the cancer cells evidently favours their dispersion at the periphery, that takes place, here, through the extension of the cancer into the unresisting, open lymph tracks. I say lymph *tracks* designedly, for the extension attacks the lymph spaces of the cutis as well as the lymph vessels proper. One might think that the extension, by means of the lymphatic spaces, was nothing peculiar, since all carcinomatous sprouts finally lie in tissue spaces, even if these have been partly opened by the pressure of the epithelium. One must therefore especially note, that, in the development of the infarctions of the lymph tracks, the extension of the cancer does not take place inside them in all possible directions, but mainly in one, and especially in the natural direction of the lymph stream. By this common direction of the epithelial stream, this form of skin cancer attains quite a peculiar and homogeneous appearance. A definite route is marked out for it; it resembles, more than other cancers, in its gradual spread, infectious processes, such as erysipelas. As already noted, this form is, in general, only present on the skin, as a secondary growth from underlying organs, and in the rare metastatic cancers;* in this we must, no

* Only rarely does a peripheral zone of simple carcinomatous lymphatic infarction, a cancerous infiltration around a cancerous nodule, surround a primary cutaneous cancer, with its characteristic structure.

doubt, seek for the explanation of the different method of growth. This different origin of the epithelium is certainly not a sufficient explanation of itself; it is not of itself comprehensible why the cancer cells, with their unlimited fertility, should not attack this strange nutrient medium in the same deleterious manner, but should, instead, advance quietly, in a centrifugal manner, by the existing routes. This difference shows us very clearly how little we know, in general, of the causes of the epithelial advance, and how weak is the previous hypothesis of the senescence of the connective tissue (Thiersch), and that of the simple pressure of tissue and growth. Probably here also—as in inflammation—some unknown, chemotactic forces play their part, and direct the epithelial masses sometimes this way, sometimes that.

So far, my experience corresponds with that of all recent investigators, that these cancers are really epithelial infarctions of the lymph track, and not endothelial cancers, which have quite another appearance. The cancerous infarctions of the skin represent, in themselves, the most innocent, slightly destructive form of cancer; it is not they, but the primary cancers (*e.g.*, of the mamma in "cancer en cuirasse" of the skin of the chest, metastatic cancers of the skin in cancer of the uterus) which cause the rapid, fatal termination of the cases. The endotheliomata of the skin have, on the contrary, their own malignant course.

According as the epithelial invasion of the skin attacks larger lymph vessels, or the tissue spaces in general, we can distinguish two forms of the carcinomatous lymphatic infarction, which cannot, however, in all cases, be strictly separated.

The *secondary degenerations* of cancerous epithelium cannot, as already indicated, serve for a fundamental division of the cutaneous cancers, but they lead sometimes to very characteristic pictures, and therefore serve, in a secondary degree, to distinguish the forms. The most frequent change is that into *hyalin*, usually concentrically arranged clumps, the so-called epithelial pearls; these were in my seventy cases seven times markedly, and about twice as often slightly developed. Especially do the fungating cancers tend to this degeneration, both the coarse reticular and the papillary, especially the latter.

To a less degree, it is found in the cylindrical reticular forms, mostly in the acinous and styloid, and in cancerous infarctions, while in the large alveolar it also appears, though more rarely. From this resumé it is evident that, for the formation of the so-called epithelial pearls, better *hyalin* pearls, a certain activity of epithelial growth is a necessary condition, and that every skin cancer certainly does not show this formation, though this must not exclude the fact that, in many skin cancers, single formations of hyalin balls, which do not go on to

definite hyalin pearls, are occasionally present. This limitation of the widespread hyalin degeneration to a few forms of cancer is all the more important, as this very hyalin formation has, recently, been very often mistaken for parasitic enclosures in the epithelial cells.

Next to the hyalin degeneration is the *simple softening* and *liquefaction* of the epithelium. This also attacks most frequently the fungating and large alveolar forms, and is often combined with hyalin degeneration. More rare is it in those cancers of the same category, which have, in addition, a tendency to the formation of horny pearls; it is never present in those which are characterised by slender epithelial processes (acinous, styloid, lymph track infarction). The liquefaction may affect minimal parts of the cancer, single cells, (Paget's cancer), or convert large sections of the new formation into a colloid or debris-like condition (colloid cancer). In the latter, not only the epithelium, but, for a considerable distance, the connective tissue also, is usually degenerated, and the appearances, in advanced degeneration, are not always easy to explain. If the liquefaction leads to tube-like excavation of cylinder-formed cancers, then the differential diagnosis between tubular carcinoma and adenoma, as well as adenocarcinoma, has to be considered. Fourteen of the cancers of my collection show some degree of liquefaction.

A much smaller number (only 8 of my cases) than is generally believed shows *keratoid degeneration*, with development of horny pearls. Their presence is limited, like the hyalin metamorphosis, to the fungating, the simple cylindrical and reticular, and a few of the large alveolar cancers, and of these, especially to those cases which affect skin regions, where the horny layer is normally thick, as the lips and the ends of the extremities. Here also we find—as in the softening cancers—mixed forms, showing both hyalin and keratoid degeneration. One may almost consider the horny metamorphosis of the cancer cells as the one extreme of the epithelial changes, the softening process as the other, while the hyalin is intermediate between them. A combination of dry, horny and softening, liquefying metamorphosis, in the same cancer, occurs only very rarely (once in my cases); consequently, though the appearances of the cornified cancer are so characteristic, they are no more to be regarded as typical of skin cancer in general, than is the clinical sign of expressible epidermic plugs.

The last change in skin cancers is the rare *calcification*, which is a metamorphosis of hyalin degeneration, and developes from this by the deposit of lime salts in the hyalin pearls.

Before we approach more nearly the individual forms, after this preliminary notice, we must shortly consider certain questions of a general nature, whose explanation will avoid unnecessary repetition in the consideration of the individual cancers.

We have sufficiently shown that the method of formation of carcinomata of the skin is extremely dissimilar, indeed that distinctly different methods of growth can be distinguished. It is therefore only to be expected that the nearer relations of epithelium to stroma should change in the most varied manner.

The very widespread view, that the unlimited growth of carcinomatous epithelium may be readily recognised, histologically, from a benign epithelial growth, by the disappearance of the normal sharp margin between the germinal layers, is therefore utterly untenable. The adenomata of the skin also cannot, at least with certainty, be distinguished from the cancers, although a tunica propria of collagenous, elastic or muscular nature is indeed present in the follicles and glands of the skin. But the surface epithelium is, notoriously, not separated from the papillary body by any membrane, and the outermost, marginal part of the papillary body, consisting of peculiarly altered collagen, varies in its thickness, according to age, region, and individuality, to such a degree that one cannot ascribe any value to its existence in individual cases. It is, in general, much easier to determine, that the margin of the epithelium varies in sharpness in almost every case, than to demonstrate wherein this marked difference, in different forms of cancer, consists. For this relation of the tissue varies not only from case to case, but even considerably in the same section.

There is a whole series of factors, of importance in this connection, both on the side of the epithelium and of the connective tissue. So far as concerns the epithelium, there is developed the appearance of a relatively normal and therefore benign condition, if the outermost epithelial cells become rooted on the cutis, that is, have on their cutis extremity a peculiar basal end; in other words, when the cells become cylindrical. But we know, from the general pathology of the skin, that this cylinder form is only the result of particular pressure relation, and especially the expression of a direct increased proliferation of the epithelium at the cutis margin; the more cells there are in the lowest layer, the more markedly cylindrical are they. A regular layer of cylinder cells indicates then only a special growth, limited to the periphery of the cancerous processes, and is just as likely to be present in true carcinomata of the skin as in adenomata; indeed, it is almost characteristic of the simple cylindrical form and its modifications, the reticular and acinous, while in the styloid it is altogether absent. It may also be developed in the fungating form, although, on account of the broad epithelial vegetation, it is only partial, while the alveolar cancers only rarely, and the lymph track infarctions never present this form of epithelium.

The less a basal cylinder cell layer is developed, therefore, in in-

creasing degree in the fungating and alveolar forms and the lymph track infarction, the more the epithelial margin corresponds to the abnormal conditions which are characteristic of cancer in general. The basal cells are cubical or polygonal; polymorphous. Whether in these cases also the margin is clearly defined, depends on the condition of the neighbouring connective tissue.

From this median position the relation of the epithelium is again changed in the styloid cancers, in which the epithelium shows traces of the secondary action, induced by the pressure of the connective tissue, by which the margin is naturally made sharper in certain directions, in others, less so.

The behaviour of the connective tissue also varies. Most different from the typical formation of the papillary body, are the margins of those carcinomata, where the epithelial processes penetrate the lymph spaces and lymph vessels, and lie along the connective tissue bundles, which show no special reaction to this invasion. But where this takes place, where old fibrillary, non-cellular, merely displaced tissue is replaced by cellular, new-formed tissue, then more normal conditions are again developed; there is then found, between the plasma or spindle cells of the zone of reaction and the basal epithelium, here and there, once more, a pale, fine, marginal line, as in the normal papillary body. But where the reaction of the cancerous invasion induces more severe symptoms, where especially many leucocytes and mast cells penetrate into the epithelium, then this sharper definition is once more obscured.

Since, however, all those factors, in any given case, may vary in the same section, there results a great variety in the relations between epithelium and stroma; from the sharpest conceivable separation of the embryonic layers, up to the existence of an indeterminate marginal zone.

A further question of general interest in connection with carcinoma of the skin, is the *reaction of the vascular connective tissue.* This has been noted by all investigators. For a time, following Virchow's lead, much stress was laid on the new-formed cells in the connective tissue, which were regarded as the mother cells of the cancerous tissue proper. This epoch came to an end with the recognition of the epithelial nature and origin of the cancerous tissue; but still, in many quarters, the presence of an inflammatory infiltration around the cancerous tissue is insisted upon, chiefly with the idea that a weakness and very frequently a benign inflammation of the normal tissue, here the cutis, tends to, perhaps must precede every cancerous invasion.

The modern, improved methods of staining, which enable us better to separate the different varieties of connective tissue cells, enable us to take up this question also and to answer it. We have then, on the

skin cancers, first to determine, whether a cellular infiltration of the surroundings of the cancer is constantly present, and then of what nature this is: and a resumé of them will alone determine this.

Of seventy cases, there are only very few entirely without cellular infiltration around the cancerous processes; but this presents very great variations. In twenty-nine cases the collection of cells in the immediate neighbourhood of, or at a little distance from the cancer, is very striking, and the most innocent, slowly-growing varieties, such as Rodent ulcers, Paget's cancer of the nipple, the cancer of Atrophoderma pigmentosum, a superficial cancer of the cheek, &c., are especially illustrative of this. In general, the further surroundings are certainly more moderately, but still more regularly infiltrated than the immediate neighbourhood, and it is only very rarely that every single nodule of epithelium is surrounded by a mantle of cellular infiltration. More frequent are the cases where the new formation, as a whole, appears to be separated by a broad wall of infiltration from the healthy surroundings, while the connective tissue bundles, which run through it, are poor in cell infiltration. I only found ten cases entirely without infiltration, and these were especially the secondary and metastatic lymph track infarctions, and then the alveolar forms. Of the cylinder forms, the styloid and acinous present moderate or slight infiltration, while the reticular and fungating forms, with the exception of the centrally liquefying, lead to severer infiltration of the cutis. But it is impossible to establish a definite law, for exceptions are always turning up. Only one definite rule stands out from all our observations, that the cellular infiltration of the cutis increases with the activity of the epithelial growth, when the epithelial connective tissue margin is the seat of marked proliferation. To the absence of this last circumstance may be attributed most of the exceptions, in which voluminous epithelial masses lie in but slightly altered cutis (alveolar, liquefying, infarctive, many fungating forms). So much, however, is absolutely certain, that the cellular infiltration of the cutis is no *essential* condition to the development of skin cancers, and certainly does not prepare the ground for them. Further conclusions we must await in the examination of the individual cell forms.

For this purpose I could only completely use twenty-eight cases, for the others were old preparations or had not been directly hardened in alcohol. This method of hardening is, for carcinomata, absolutely essential, since the *main part of all the cellular infiltration in them consists of plasma cells.** These are found, in the further surroundings, pretty equally divided, singly and in small collections, and often

* Half of the cases (14) had their processes surrounded by very distinct accumulations of plasma cells.

gather themselves into a shell-like layer around the carcinoma, immediately round the epithelial growth. From here, there extend, in a few cases, thicker cords between the individual epithelial reticulæ, close up to the sub-epithelial marginal layer, thus filling all the spaces between the epithelial tissue. But oftener we see, in the immediate neighbourhood of the epithelium, only single plasma cells.

Where they are present in moderate numbers, the plasma cells are mostly well developed, but not especially large. The closely-packed masses of cells are, on the contrary, chiefly formed of very small plasma cells, which evidently represent the areas of wandering cells, of many authors. Good protoplasm staining will prevent one from falling into this mistake. The infiltration then is formed, in its outer parts, of large plasma cells, in its inner, near the new epithelium, of masses of small plasma cells. Where no secondary inflammation is present, the emigration of leucocytes, in general in cutaneous carcinomata, is very slight. One may speak definitely in this matter, since the broad epithelial processes present a very readily observable field. Were the emigration of leucocytes in any way marked, the carcinoma nests would everywhere swarm with stationary leucocytes, like the epithelial sprouts in most inflammatory dermatoses. But this is only here and there the case, and is then possibly to be ascribed to secondary traumatic or therapeutic action, to which most carcinomata of the skin are exposed; for they are found more often in the warty, papillary forms than in all the others.

The absence of local leucocytosis is all the more striking, as another form of cell is evidently attracted by the carcinomatous processes in the epithelium—namely, the mast cells, which otherwise usually appear stationary. The increased number of mast cells has been long known, but it is evident from my preparations, that in skin carcinoma the mast cells are of that form of connective tissue cell, which is most constantly met with increased. The mast cells are found, in definitely increased numbers, in those places where all formation of plasma cells and all other cellular infiltration is absent; this of itself is by no means striking. It is the normal habit of mast cells to form or to group themselves around the epithelial processes; and most processes which are combined with epithelial growth, lead to an increase of the mast cells in the immediate neighbourhood of the epithelium.

In the distribution of the mast cells, we certainly find a similarly capricious arrangement as in that of the plasma cells. It is not always the immediate neighbourhood of the epithelium which they prefer, but the further surroundings are sometimes equally, though sparingly, permeated by them. In some cases they are collected in masses, even under the still healthy surface epithelium, surrounding or covering the

carcinoma, while they permeate the cancer itself only in moderate numbers. But their close relation to the process is shown most definitely in the certainly infrequent cases—mostly fungating cancers —in which they, like the leucocytes, penetrate into the lymph spaces of the carcinomatous epithelium, and are seen swimming in the liquefied portions of the cancer. Apart from its relation to the cancer process, this is naturally of importance in considering the nature of mast cells; we learn from it, definitely, that elements of the connective tissue, originally fixed, may, after taking up certain specific granular constituents, become, under the influence of a special chemotaxis, movable. The remarkable, twisted-looking form of many mast cells, as well as the free mast-cell granules in their neighbourhood, had already made the motility of these cells probable. Finally, in order to give an approximate idea of their quantitative relation to skin cancers, I note, that, of twenty-eight cases, thoroughly examined, in ten their number was extraordinarily large, in as many more it was moderately great, while in the rest only a slight increase had taken place, no more than in any other inflammatory process. They were never absent, nor so few in number as in the normal skin. But they never formed—however great their number—closely packed areas, as they do in Urticaria pigmentosa, or as do the plasma cells of the same preparations. Finally, it is to be noted that, in some cases, a sort of opposite proportion was evident between mast cells and plasma cells; often quite small nodules (carcinoma of the cheek, several carcinomatous warts in sailor's skin, a cancer of the glans) were surrounded by a dense collection of plasma cells, and only a few mast cells, while other cancers (a melanocarcinoma, a rodent ulcer, a carcinoma gelatinosum) only showed a few plasma cells, along with an exceptional number of mast cells. But in other cases again the presence of both varieties was proportional.

In addition to these varieties of cells, there are occasionally a few giant cells—or better, "chorio-plaques"—whose presence I was able to determine in a carcinoma of Xeroderma pigmentosum. Here, close around the tumour, a number of plasma cell collections had been transformed into these multinuclear large structures.

If we sum up these facts, we find that we have, in about half the cases of skin cancer, a plasmoma formation in the cutis, which recalls certain infectious processes, like diffuse lupus or many syphilides. The occasional formation of giant cells further favours this resemblance. The striking participation of the mast cells points to the fundamental rôle of an epithelial growth. An infectious process in the epithelium —that is the general view which we deduce from the above observations, and it should lead us not to separate the skin cancers too widely from other chronic infectious processes. In particular, this view of the

skin cancers is necessary, as opposed to the sarcomata,* which present quite another type of connective tissue cell, and by no means resemble the so-called granulomata.

We come now to a third and important point, of more general interest, which, up to now, has been somewhat more cavalierly treated than the nature of the connective tissue cells in cancer—viz., the *structure of the cancerous epithelium itself.* We have already recognised, in separating the alveolar cancers as a special and by no means predominant group of skin cancers, that certain elementary qualities must be present in the cancer cells, whose variations bring about the great differences in the gross architecture, especially between the fungating and cylindrical cancers on the one hand, and the alveolar on the other. If we provisionally define these fundamental qualities, greater or less motility, from a physiological standpoint, there arises the important question, whether we can find histological criteria as a sure basis for the acceptance of these changes. And this, as a matter of fact, we can do. We only need to stain the epithelial cells, not in the ordinary way with nuclear stains, nor in the way recommended by me for staining protoplasm, but in such a way † that the epithelial fibrillation of the prickle layer is specially demonstrated. We then see at once the connection of the prickle cells with each other, and that of the epithelium of the cancerous processes with the surface epithelium. If sections, from different skin cancers, are examined with this in view, for example, those from cylinder-formed and alveolar cancers, and compared with one another, it is evident that very great differences are present. The firmer the structure of the cancer, the better is the fibrillary structure retained, and all the better are the connecting bridges between the epithelial cells developed. The looser the epithelial processes are, the more difficult is it to demonstrate the epithelial fibrillation and the prickles, and in the alveolar cancers they are altogether absent. Wherever large, round epithelial cells are snared off, singly or in groups, from the surface epithelium, we may be pretty sure that at this place the general epithelial fibrillation stops abruptly. The young epithelial cells have then attained a new structure of their own; in place of the circular loops and the radiating threads, they show a uniform, finer or coarser net of protoplasmic threads, in the centre of which the nucleus is suspended. They resemble, in this net-like frothy arrangement of their protoplasmic threads, the large spider-shaped cells of the connective tissue, or still better, many simple, glandular epithelial cells. As in those, they have of course a greater

* I except the figured Sarcomata, which must be distinguished from the Sarcomata proper.

† Water blue orcein method, acid fuchsin picrin method (s. under), Gentian-violet iodine method, Kromayer.

individuality, and a less dependence on the neighbouring cells and the epithelial tissue as a whole. This invariable observation confirms the hypothesis of a greater power of motion of the epithelium in the alveolar cancers, which was suggested above.

It is not unimportant, and it confirms this experience in cancer, that a perfectly similar process—as we shall see under nævus—accompanies the snaring off of the nævus cells from the epidermis, in early life. There also, the prickle cells of the surface, with their distinct epithelial threads, are converted, at a definite point, somewhat suddenly, into soft, loosely connected "nævus" epithelia, and this structure they retain during life. It is then no wonder that it is alveolar and not cylindrical cancers which are developed from them.

We are here confronted with a general law, of pretty wide application. While the idea of the metaplasia of mesodermal cells into ecto- and endodermal epithelium has rightly lost support, it appears to be a tolerably widespread view, that the peculiarities of the epithelial cells of squamous, glandular, and cylindrical type, must be tenaciously retained in their pathological products. But this is certainly not the case in the epidermic epithelium. A whole series of pathological processes actually depends on the change in the form of the epithelium. The most important is certainly that of the loss of the fibrillation, so necessary to the epidermic covering; for the fibreless, soft, epithelial cell is capable of assuming any other form of epithelium, such as that of acinous or tubular glands, or of cylindrical epithelium. In a very interesting tubular carcinoma, developing from the surface epithelium (see below), I found on the ends of the epithelial taps, fibreless epithelial cells developing, and in these, after the development of a lumen, the innermost formed a regular cylindrical layer. As problematic as a metaplasia of the derivatives of the different embryonic layers is, so certainly is there a *metaplasia of the epithelial forms*, under pathological influences.

I.—Fungating Forms.

(a). *Papillary.*

The chief seat of the papillary cancer of the skin is the glans penis, and next, the skin, at its junction with the mucous membrane of the lips. A luxuriant proliferation of prickle cells of a stabile character is necessary to the development of this, as of all fungating forms, but a further necessary is the absence of a firm covering, which compels the epithelial masses to penetrate into the depth of the cutis. If this is present, there develope the deep, fungating cancers of coarse

reticular type, which form the next section. But when it is absent the epithelial masses collect on the surface, and then form greyish-red, thick masses, which, as cornification advances into the depths of the epithelial taps, gradually become folded, and, on the surface becoming softened, separate into a number of papillary elevations, and take on a cauliflower appearance. The thin horny layer at the apices of the papillæ frequently tears and desquamates, and there then ensue hæmorrhages, exudation, crust formation, and partial necrosis of the surface; the papillæ then appear red and strawberry-like, covered with slimy yellow masses or crusts. The connective tissue, remaining between the broad epithelial processes, is usually in the form of thin, long, vascular papillæ, swollen with œdema at their apices, or of still finer, pointed ones without blood vessels. These may be simply or multiply subdivided by secondary epithelial invasion, or, by secondary union of the epithelial processes, may become net-like, thus losing their papillary character.

It is hardly any longer necessary to state, that these papillæ have nothing necessarily in common with the normal papillæ of the skin, whose site they occupy, that at least—as is unfortunately still stated in many recent books—they do not represent hypertrophy of the normal papillary body. Usually the "papillæ" of the cauliflower growth are much less in number than the papillæ of the same area of healthy skin; a large proportion of the normal papillæ is flattened out at the first attack of the epithelium and only a few of them are retained, and these gradually become longer (not in general larger) the more the epithelial ridges increase. But even where no papillary surface is present, the epithelium, by its irregular growth, excavates "papillæ" in the cutis, and in these again, irregular, so-called mother and daughter papillæ. The papilla is then, pathologically, only a "marginal phenomenon," not an independent "histioid" type, like the blood capillaries; there are no "papillomata" as there are angiomata, but only papillomatous tumours, and therefore also papillary cancers.

As the epithelial masses collect themselves on an area of skin, which gradually becomes too small for them, the tumour developes a radiating, fan-like form, the epithelial processes being broad on the surface, but at their lower ends much smaller, and pressed together. The form also of the single epithelial cells, near the surface, is more similar, and their size much greater than at the base of the epithelial process, where the pressure of the tissue has a distinctly limiting influence. As the cylinder form of the basal epithelial layer is not only related to the new formation of epithelium, but is equally related to the disposable area of the surface of the skin, there necessarily results a very varied development of the cylinder cell layer. Deep down at the points of the processes it is usually well developed, much less at

the upper parts of the papillæ, where the neighbouring epithelial cells have more room, and better again where the local formation of mitoses has been greater. If the epithelium finds an outlet in the development of new processes and the opening up of new connective tissue surfaces, the palisade basal layer is once more less well developed, &c., &c. And therefore, in the papillary as in the fungating cancers in general, proliferation is not strictly limited to the connective tissue margin, but takes place also inside the epithelial processes. Where this latter predominates there is naturally no basal cylindrical layer.

In so far as the existence of a regular cylinder cell layer may be considered characteristic of normal young epidermis, and indeed always gives the impression of a sharp margin between the two embryonic layers, it is important to make clear, that, in this first form of cancer, its presence is altogether irregular, and that it has nothing to do with the "wild growth of the epithelium," but is solely dependent on two factors,* which have no near relation to the malignity or benignity.

The epithelial cells of papillary cancer are always well-developed prickle cells, usually of considerable size. They tend to the formation of hyalin pearls (glans penis) and of horny pearls (lips), those of the surface to cellular and inter-cellular œdema. The uppermost layer of cells, under the influence of secondary immigration of micro-organisms, necroses more frequently than in other forms. This is no doubt due to the fact that, on account of their folded surface and their situation, the papillary cancers suffer much from external injury. We find, almost invariably, emigration of leucocytes, and small hæmorrhages at the apices of the papillæ; both are no doubt caused by the stagnation of blood and lymph, which is induced by the increased tissue pressure on the usually ensnared base of the tumour, and finds its histological expression in the dilatation of the blood and lymph capillaries in the apices of many papillæ.

The cellular infiltration in papillary cancer is usually not marked, and is limited to a small, though dense zone of plasmoma, which sends out fine processes into the small papillæ, but rarely so far as their points.

The papillary carcinomata are rightly considered malignant, for they can only be formed by epithelial growth, which is active from the commencement. But, on the other hand, in the first stage of their existence, and before there is any swelling of the glands, the prognosis is very good, for they are more easily completely removed than other cancers, so long as they retain the pure papillary superficial character.

* The number of well-developed cylinder cells is directly proportional to the number of mitoses at the connective tissue margin, and indirectly proportional to the surface of the latter.

(b). *Coarse reticular.*

The simple, fungating carcinomata of coarse reticular form develope either from, or in conjunction with papillary forms, by the deeper in-growth of the epithelium. In the latter case they show a more or less papillary, folded surface, in the former they consist mostly of solid, smooth or irregular nodules, which are mostly eroded in the centre, and appear at the margin elevated like a cushion. Here and there, but certainly not invariably, there are found, at the edge, expressible horny plugs. They are mostly carcinomata of the lips, the cheek, and the nose, and ten of my cases belong to this type. One was a deep carcinoma of the penis.

All consist of more or less voluminous epithelial processes, arranged in loops, often indented and angled, and connected by innumerable buds and bridges into a uniform, net-like arrangement, usually sharply marked off from the connective tissue. The origin of the cells from the prickle layer of the surface and the follicles is as easily recognisable as in the papillary forms. At parts of the surface a papillary character of the connective tissue is now and again present, but it is usually reticular throughout, like the epithelium. The coarser the reticulæ of the latter, the finer are those of the connective tissue net. In parts, the epithelial net so predominates that, in the section, only quite small, rounded or slit-like islands of connective tissue are visible, which do not all contain blood capillaries. In other cases these are larger, irregularly formed, and contain, in addition to the blood vessels, a dense infiltration of plasma cells, and a lesser number of mast cells. As the epithelial processes mostly present a convex surface to the connective tissue, the islands of connective tissue between them generally show a concave, festooned contour; giving one the impression of an unresisting, passive tissue.

These coarse reticular carcinomata provide the best means of studying the different forms of epithelial degeneration, for the epithelium in the centre of the voluminous process is beyond doubt insufficiently nourished. In almost every case there are found hyalin pearls; more rarely horny pearls. But the central softening is especially characteristic of this form. It leads to circumscribed cavities, or to a systematic tube-like excavation of the epithelial net. The softening is often combined with the hyalin, less often with that and the horny metamorphosis. As the softened and rarefied epithelial masses usually stain more faintly than the well-preserved marginal parts, it is often not altogether easy to distinguish these central areas of softening from the connective tissue islands, surrounding the periphery of the epithelial processes. It is only easy where the epithelium is marked off from

the connective tissue by a regular layer of cylinder cells, or at least by vertically arranged epithelium. But such a sharp limitation exists only here and there, as in the papillary cancers, although in general more frequently. Confusion, however, will only occur with a simple nuclear or protoplasmic stain, by which the epithelial cells, which are softened and run together to a homogeneous mass, remain unstained, like collagenous tissue. A special staining of the collagenous fibres prevents all mistakes.

A further feature, which many of these cancers show, is a limited leucocytosis which only takes place in the softened or pearly degenerated parts, and is evidently induced by the degeneration of the epithelium.

The new formation of the epithelium is, in these carcinomata, distinguished by a great number of the most typical normal mitoses, which are, in general, distributed in the peripheral parts of the epithelial reticulæ, but are by no means limited to the layer next the connective tissue.

The reaction of the connective tissue in the coarse reticular cancers is more active than in the other forms. But usually only the nodule as a whole is enclosed by a plasmomatic halo; in the larger connective tissue reticulæ of the interior of the node, there are only a few collections of cells, and the small, slit-like spaces are almost always free from cellular infiltration. The mast cells, on the contrary, are present in moderate or considerable amount all through the node, and often penetrate into the epithelium. The coarse reticular cancers are particularly suited for studying this important point in the history of the mast cells.

II.—Cylindrical Forms.

(a). *Reticular.*

Though I have given above, as the chief distinction of the cylindrical carcinomata of the skin, the almost cylindrical form of the epithelial processes and the limitation of the mitoses to the epithelial layer lying next the connective tissue, it is still clear, in view of the irregular growth of all carcinomata, that these differences are of especial importance, when they are found to affect all parts of the tumour. In particular, this form of "simple reticular" cancer frequently shows transitions to the fungating form of the "coarse reticular," more than the later cylindrical types. But on this very transition form it may be noted, that in the formation of the smaller cylinder form we are dealing with a new principle of epithelial growth. We see small sprouts growing out of broad composite processes, which

contain, in their centres, epithelial pearls; these first appear as small buds, and later as cylindrical branches, which consist of small and deeply-stained epithelial cells. They may unite and form, between the original, large epithelial processes, a secondary, finer net, or they grow independently, in the finer form, deeper into the tissues.

In order to explain this limitation of the, in the fungating forms "unbounded," growth to single chosen points of the periphery, it is not sufficient to assume a more limited power of proliferation of the epithelium; for this would not explain the change in form of the epithelial processes. But we must especially assume a limitation of the epithelial growth on behalf of the cutis, which in general opposes a considerable resistance to the proliferation of the epithelium, and only permits its further entrance into the connective tissue where it is most actively proliferating, thus leading to an outgrowth of the germinal layer of the epithelium. As a fact, all these cancers present in the cutis signs of a greater resistance than usual, either in the form of a specially dense cellular infiltration between the epithelial processes, or of firm, newly-formed, collagenous tissue. In the reticular form here under consideration, it is usually the former, in the cylindrical cancers, the latter.

Macroscopically, the reticular cancers form flat, plate-like, softish nodules, which do not extend deeply into the tissues, and are not very sharply defined. They correspond to the old type of "infiltrating cancers." The thicker parts of the epithelial net completely correspond, in regard to the variety of cells, mitoses and degeneration products, to the coarse reticular, and they frequently contain hyalin pearls. The finer trabeculæ, which make up the greater part of the tumour, and in the pure form completely compose it, show, on the contrary, a regular cylinder layer, which presents only mitosis and no degeneration products. They end free in the tissue with knob-like, swollen ends, or, joining other parts, help to compose the epithelial net.

Like the coarse reticular, the reticular cancers always take their origin from the prickle layer of the surface and the follicle, without a separation being anywhere possible. Only, one can here, on account of the fineness of the epithelial processes, more often recognise the gradual atrophy of the sebaceous glands, and the total disappearance of all the follicular epithelium in the new growth. One finds, more often, remnants of the sebaceous glands and hairs, without a hair follicle, in the middle of the cancerous tissue.

The cutis takes a large share in the process, and the mass of plasma cells is, as a rule, in inverse proportion to its activity. Parts of the cancer, which show, in the interior of an extensive plasmoma, a fine, wide-meshed, branched epithelial net, usually vary with other parts,

in which broader epithelial masses are separated by smaller but always much infiltrated connective tissue processes. And in still another way the stronger resistance of the cutis demonstrates itself in these carcinomata, namely, in a reaction upon the structure of the epithelial cords, which is evident in all cylindrical cancers, especially in the styloid, while it is absent in the fungating forms. From the increased pressure, under which these carcinomata grow, the individual epithelial cells are not only diminished in size but changed in form. While their form in the fungating cancers is, in the middle of the epithelial processes, always circular or cubical (with the exception of the pearls and their immediate neighbourhood), here, even in the centre, long, even spindle forms predominate. In the very small processes these lie in the axis, but in the broader ones they are frequently arranged in different directions, forming all possible angles, and giving to the affected part a peculiar, ring-straked, speckled appearance. Often such divergent internal, epithelial streams may be followed outwards into particular epithelial buds and meshes of the net, and one recognises that the same resistances, which allow only punctiform sprouting of the epithelium from the periphery of older epithelial processes, also induce these displacements inside the latter. As these presumptive resistances are only of a passive nature, and do not consist in the active in-growth of the connective tissue into the epithelium, one has to look at the process thus, that the proliferating epithelial masses, which are hindered in their extension, are subjected simultaneously at many points to an internal pressure, by which the cells are lengthened in bundles in the direction of least resistance, and narrowed at right angles to this, in the direction of the nearest mitotic focus. Where such epithelial bundles cross each other at wide angles, there develope, as in the crossing collagenous bundles of the cutis, larger lymph spaces, which definitely indicate the internal tension in the epithelial mass.

(b). *Simple Cylindrical Forms.*

While the reticular cancers, here and there, recall slighter forms of the coarse reticular, fungating carcinomata, in the simple cylindrical type there is no resemblance to the first group. The epithelium here produces only polypoid, long, frequently crossing processes, of cylindrical type throughout, which, only at single nodular points, swell up to broader epithelial processes. The epithelial ends develope preferentially from the prickle layer of the follicle, but also from that of the surface. The follicles disappear in the new growth, without leaving any trace, except scattered hairs or hair cysts, as do the larger sebaceous glands,

when—as is usually the case—these cancers occupy the region of the cheeks and nose.

The macroscopical appearance of these carcinomata is exquisitely plate-like; they are sharply margined and have little tendency to superficial ulceration. Expressible epithelial plugs are never found. They appear to be in general rare; in my collection only three follow this type. In one case two suspicious tumours developed simultaneously from small nodules on the cheeks of an old gentleman; the one proved to be a typical cylindrical cancer, the other a simple hypertrophy of the sebaceous glands. The former showed very beautifully, in different parts of the tumour, the modifications of the cylindrical type, namely, on one side, a transition to the reticular, on the other, to the styloid form, so that I base the following description chiefly on this case.

The greater part of the tumour consisted of small cylindrical cords of epithelium, which permeated the whole cutis down to the hypoderm, and, as was evident from the few fragments of hair, had chiefly arisen from the follicular epithelium. They did not communicate throughout —as in the reticular form—but spread as a whole, like the branches of a tree, almost horizontally in the cutis, giving off many lateral branches, which meet and cross one another, without running together. The broadest branches are the most superficial, running horizontally under the papillary body, and here and there enclosing horny pearls, the remains of previous follicles. Those of the middle and deeper cutis are all equally small, and show only now and then rosette-like swellings, which are held together by thin stalks.

At this point the tumour is only slightly elevated, and the cutis, in spite of being permeated by epithelial cords, appears hardly increased in volume. This is due to the position of the epithelium and the absence of a marked cellular infiltration in the cutis. The round epithelial cords retract strikingly from the connective tissue tubes, in which they lie. The walls of the latter are smooth, here and there lined with flat cells, and more than in the other cylindrical cancers give the impression of newly-formed cavities. They are certainly not all lymph vessels, through which the epithelial processes have grown, but we may, with good reason, conclude that the larger horizontal tubes, and especially those running in straight lines at the margin of the papillary body, whose cavities are filled up with strikingly thick epithelial cylinders, are of this nature. The smaller lateral buds are pushed out from these lymph vessels into the communicating lymph spaces, and these are thus converted into stalk-like or rosette-like tubes. From the carcinomatous lymphatic infarctions, which will be later described, the cylindrical form differs in the firm structure of the cylinders

themselves, which consist of closely packed, small epithelial cells, with a peripheral cylinder layer and the formation of mitoses, and in the fact that the collagenous bundles, as a whole, persist and are not penetrated by the epithelium.

This retention of the pre-existing connective tissue is a further distinction of the cylindrical cancers. It is evidently connected with the slight formation of young connective tissue cells in them. Only the spindle and mast cells are increased in number, and in the larger islands of connective tissue, which contain blood vessels, there are found very small collections of plasma cells. Otherwise the connective tissue is only little affected, chiefly only mechanically deformed. The appearance of the elastic fibres, which in this form of cancer is quite characteristic, definitely confirms this view. The elastic fibres are all perfectly preserved, and closely pressed on to the connective tissue bundles, so that by appropriate double staining (orcein, hæmatoxylin) the epithelial cylinders appear to be directly enclosed in a thick elastic net. Only at a little distance is the tumour surrounded by a rich new formation of plasma and mast cells.

This true, simple, cylindrical type undergoes, in certain places, modifications in two directions. First, the tumour mass grows more vigorously at one point, and elevates the epidermis over it, or it may penetrate it. Here, in the upper half of the cutis, the microscope shows a transformation of the cylindrical into the reticular type, while the original form is retained in the lower half. The epithelial cords are not only broadened, but shoot out buds in all directions, and thus run together into a true net, with broad reticulæ and narrow meshes. The remaining connective tissue is reduced to fine bundles, but the greater part of it has disappeared, having been absorbed with its cells. This disappearance is most evident on elastin staining, which demonstrates the absence of the close elastic net. In the thickened epithelial processes there appears, in most places, that "internal tension" and bundle-like arrangement of the elongated epithelial cells, described above in the reticular cancers. Now and then we recognise the first commencement of the softening process. This manner of transition illustrates, I believe, in the simplest way, the connection and the difference between the simple cylindrical and the reticular cancers.

On other parts of the tumour, which are as flat as the chief part, a further development has taken place in the opposite sense; the connective tissue stroma has become thickened, at the expense of the epithelial processes. The large spindle and mast cells have disappeared from the connective tissue septa, as has all elastic tissue. Instead of these, a new fibrillary tissue, with numerous flat cells, has developed, which not only presents to the epithelial growth greater resistance, but

converts the epithelial cords, which were at the commencement like round stalks or rosettes (convex), into concave, much excavated, pointed processes. From the simple cylindrical form developes the styloid, which must be more closely considered by itself. This variety in the epithelial formation consequently takes place with simultaneous changes of the constituents of the cutis, so that an alternation, or a common dependence of both on a third factor, cannot be disputed.

It is finally to be noted, that the slight plasmoma development, in the scaffolding of the simple cylindrical type, is so flattened out that, in the neighbourhood of the tumour, a pretty distinct shell of plasma cells is developed, and further out many small, scattered plasmoma areas.

(c). *Acinous Forms.*

The Acinous is the rarest form of the cylindrical cancers (2 of my cases), and differs from the simple cylindrical only in the more regular budding of the ends of the epithelial processes. But it is from this that the carcinoma acquires its peculiar acinous type, which justifies the separation of this form. The point of origin was, in one case (lip), the prickle layer of the surface, and the large hairs of the beard; in the other (nose), the lanugo follicles, chiefly consisting of sebaceous glands.

In such cases, on account of the richness of the affected region in sebaceous glands, the total disappearance of the latter at the seat of the tumour, and the acinous form of the epithelial new growth, distinctly suggest a special sebaceous gland cancer. But more thorough examination shows that all the prickle cells of the region may take part in the formation, and in individual cases only those chiefly present form the chief part of the cancer. It shows, further, an influence of the pre-existing structures on the formation of the cancer, in the sense that the spaces, which they previously occupied, are soon completely filled with cancerous tissue, and thus, especially in sebaceous regions, sebaceous gland-like cancer masses are developed. But this does not continue, and the later developed epithelial masses show a distant resemblance to acinous glands, only because a number of rounded buds simultaneously spring from neighbouring areas, and in this way cluster-like nests are developed.

On this latter circumstance alone, on the collective budding of spherical, conical or semi-spherical, solid epithelial buds, which remain stationary at this incomplete stage of development and do not develope into reticular cancer, depends the peculiar nature of this form.

The mitoses are, as in the simple cylindrical type, distributed at

the periphery. The reaction of the connective tissue consists, as there, only in a swelling of the pre-existing spindle cells and a multiplication of mast cells. No greater degeneration is present. As smaller enclosures in the cancerous tissue, we find a few hyalin cells, a few remaining sebaceous cells, and here and there a lanugo hair.

FIG. 25. Cylindrical Carcinoma of Cheek; showing transition into the Acinoid, Styloid and Reticular Forms.

(d). *Styloid Form.*

The styloid cancers partly develope, as I have just indicated, from other cylindrical cancers. Such a secondary transition in isolated parts of skin cancers appears to take place often; in my collection I have three instances. At these places the cancer assumes a more benign appearance and no doubt nature; the epithelial new growth is arrested under the influence of fibrous, one may say scirrhous hardening of the cutis.

Of especial practical interest are those cancers, which, from the commencement, present only styloid epithelial buds. A quite distinct group, of well-known benign character, Jacob's carcinomata, the true Rodent ulcers, shows this type most perfectly. But other cases also belong to it, cases which have clinically received the simple definition of cancer, and are distinguishable, histologically also, from Rodent ulcer. The definition of primary styloid cancer is therefore a wider one than that of Rodent ulcer, although, in my experience, all Rodent ulcers belong to this type. But if we deduct all Rodent ulcers, as well as all other cancers, which only here and there show a styloid transformation, there remain, of the cancers of my collection, only two styloid cancers proper, one of the nose and one of the lip.

Both are developed from the prickle layer of the epidermis, that of

the nose from the follicular epithelium also. In both cases we note, at the first glance, two conditions, which are combined in all styloid cancers; the extraordinarily small, delicate epithelial processes, terminating in pointed ends, and the firm fibrillary stroma, in which they are embedded. The latter is also rich in cells, but only in those swollen or simply increased spindle cells, whose appearance accompanies fibrous new formation. Plasma cells are altogether absent in the stroma of the cancer, and elastic fibres and mast cells are only sparingly present. Further out, at the margin of the fibrous new formation, we may certainly find a few collections of plasma cells; a distinction to Jacob's ulcer, where the surroundings swarm with plasma cells. In the neighbourhood of the epidermis the epithelial processes have a perpendicular, ascending direction in the cutis, and in the hypoderm they radiate in all directions, frequently horizontally. They are separated and at the same time enclosed by relatively broad septa of swollen connecting substance, whose convex form is reflected in the concave excavation and pointed processes of the epithelium. To the smallness and the excavation of the latter there is further added, as a third pressure phenomenon, an "internal tension" of the elongated epithelial bundle, which, from the lesser calibre of all the cylinders here present, certainly never has the speckled surface which is seen in reticular cancers.

Mitoses are rare in the styloid cancers, corresponding to the slow new formation of epithelium, as are epithelial degenerations, so long as the styloid character is preserved. Only in individual, swollen, nodular points of the epithelial processes, do we see, now and again, a single hyalin or liquefied cell. But the epithelium over the new growth has a distinct tendency to be here and there elevated. The uppermost styloid processes then lie bare, interrupted by islands of infiltrated cutis, but with a strong tendency to undergo afresh a cornification of the whole surface, of a more or less temporary character. In this also, these cancers resemble the Rodent ulcer.

III.—Alveolar Forms.

(a). *Large Alveolar Forms.*

As already indicated in the introduction, the large and small alveolar forms are not sharply distinguished. Certainly the latter exist pure, which the large alveolar rarely do, since, in the neighbourhood of the large cancer masses, there is present a number of smaller ones which unite them. The large ones are hardly to be otherwise viewed than as caused by a stoppage in the further dispersion of the

epithelial cells and the proliferation of those already present. But still they retain the alveolar type; they form enclosed areas, gifted with independent growth, and without any other than an accidental connection with the neighbouring alveoli. Such may, for the sake of example, be induced in their further course by the disappearance of the interstitial tissue through pressure. The chief contingent is supplied to this type by the unpigmented and melanotic carcinomata, developed from nævi. But as they deserve, on other grounds, special consideration, we may here pass them over, and there remain only a few carcinomata of the skin, which represent this type (from my collection only two ordinary cancers, from the knee and neck, of which the latter showed a transition to the small alveolar form). They are sufficient, however, to lead up to an understanding of the peculiarities of these alveolar cancers, by a minute examination of the forms of the cell; in this the size of the cells plays an important part.

I have already shown the relation of the greater scattering of the young epithelium, at the periphery of the nodule, to the development of the alveolar growth, and hypothetically ascribed their distribution to a peculiar motility of the cancer cells. Here is the place to examine how far the histological characters of the cancer cells, here present, support this hypothesis.

Even with the low power the rounding off of the individual areas is striking, since it does not, as in the cylindrical and many fungating cancers, represent a more active proliferation at the periphery of the area, and a well-marked cylinder layer. This nowhere exists. The rounding off of the individual areas is rather to be ascribed to a swelling of the individual cells, which, striving to attain the circular form and thus flattening and pressing on one another, actually assume cubical and polyhedral forms. An alveolus has therefore most resemblance to the acinus of a mucous gland, and is as different as possible from the usual tap or cylinder type.

While this form of the cells points to a certain softness of the epithelium and its approach to the form of mucous membrane epithelium, further examination shows further differences of the internal cell structure. However good the staining method used (acid fuchsin, picric acid, water blue orcein method) no epithelial threads are to be discovered. The external cell prickles are also absent; the cells lie close together, with fine zig-zag or smooth borders. The scaffolding of the epithelial cells is therefore not thread-like, but exquisitely frothy, and one can, in most cells, distinguish a coarse-meshed, loose, internal, from a small-meshed, denser, external zone. These cells are not so much predisposed to the separation of a firm internal zone, with the nucleus, in the form of hyalin clumps, as to the complete liquefaction

of the internal zone, with the development of balloon-formed cystoid cells.

I tend to regard the absence of the epithelial threads and the continuity of the cells, represented by the prickles, on the one hand, the nearly cubical, facetted form of the epithelial cells, even at the connective tissue margin, and their greater softness, on the other, as the basis of the alveolar form of these cancers. Like Ranvier, I see in the epithelial threads not the proper active protoplasm of the epithelial cells, but only a special arrangement for the firmness and resistance of the epithelium of the skin. It is certainly in favour of this, that the epithelial threads are absent in the cutaneous epithelium of the embryo and are lost in many cancerous growths. If one wishes to ascribe to certain skin cancers a special juvenility, an approach to the embryonic conditions, and a specially limitless growth, the alveolar cancers come nearest to this condition, certainly nearer than all other skin cancers.

It is not against this view of the alveolar cancers, that, even among the other forms, especially the fungating and lymph track infarctions, individual cases are present, in which the softer and more independent cell type, just described, is here and there developed. In the fungating cancers there are such places, which show no well-formed cylinder cell layer and no tendency to the formation of horny and hyalin pearls. And we frequently find, in the neighbourhood of the connected epithelial net, detached nests of alveolar formation. In the description of the cancerous infarctions of the skin we shall see that these are often difficult to distinguish from the small alveolar type. But these exceptions, which are never present in the cylindrical type, only confirm us in distinguishing a special alveolar form of cancer, although pure cases are relatively rare in the skin.

The independence and size of the epithelial cells, in the large alveolar forms, is an additional cause why we find here such well-developed, voluminous and complicated forms of mitosis. In a carcinoma of the knee, of this form, for which I thank Dr Török, I have met with the largest examples of mitosis, in skin cancers, but they were only rarely irregular in form. The latter were certainly too few to be regarded as characteristic of the tumour. The irregularity mostly consisted only in a superfluity of loops or a few irregular loops. Triple and quadruple mitoses were very rare. That in their presence, a causal significance for the abnormal growth of the cancer, as such, is present, is unlikely, on account of their great rarity in skin cancers. I have only found these irregular mitoses in alveolar cancer of the skin, never in those fungating luxuriantly.

Further, the carcinoma, with which we are dealing, tends to

liquefaction on the one hand, and to the development of very large, multinuclear, epithelial giant cells on the other. In both points the other large alveolar carcinoma of the neck resembles it, but it presented no irregular mitoses. The liquefaction is in both partly endo-epithelial, and then affects always the inner part of the cell, which, in the smaller mono-nuclear cells, leads to simple peri-nuclear cavities. In the multi-nuclear large cells all, some, or only one nucleus may lie in a large vacuole, developed by liquefaction of the protoplasm. Further, liquefaction of whole epithelial cells leads to larger cavities between the cells, usually in the middle of the alveoli, which are filled by a fluid, rich in albumen, showing, when stained with methyl-blue, fine, blue stained granules, a few nuclei and fragments of protoplasm, and now and again containing threads of fibrin. Leucocytes are only met with exceptionally in these cavities. In the latter case it was possible to stain for plasma cells, and it was evident that the whole carcinoma was marked off from the surroundings by a pretty broad plasmomatic zone. Mast cells were present in moderate quantity. This carcinoma of the neck showed most beautifully the transition to the purer alveolar; the small alveolar form. At those places where the alveoli become smaller and are finally reduced to single epithelial cells, to which, strictly speaking, the name of alveolus is no longer applicable, the character of the cells remains; they retain their equally round or cubical form, the marked size of cells and nuclei, and the absence of epithelial threads and epithelial connection. If the whole section is shaken, the small alveoli, like the large ones, become empty, their contents for the most part fall out and leave behind them, there a coarse, here a fine-meshed connective tissue scaffolding, which, the nearer it is to the periphery, is the more infiltrated by swollen spindle and mast cells.

(b). *Small Alveolar Form.*

This type is found pure in four cancers of my collection, two Paget's cancers, which I owe to Sir James Paget, one cancer of the sole of the foot, which Dr Török procured for me from the Pesth collection, and a true cancer of the sweat glands, some sections of which Dr Darier kindly gave me.

The characters of the alveolar cancer are here represented as in the large alveolar type; only the alveoli seldom exceed a diameter of four to six epithelial cells. The individual epithelial cells are also not so large, while in their rounded, cubical, facetted form they resemble glandular rather than surface epithelium. In one of Paget's carcinomata the small cancerous alveoli are directly continuous with the cancerously degenerated

prickle layer of the surface, by means of irregularly divided processes, which stretch perpendicularly downwards. In the other case the alveoli are mostly winding and closely pressed together, so that the whole section has a gyrate appearance, resembling the surface of the brain. The connective tissue scaffolding is, in this case, reduced to a minimum. Still smaller alveoli were seen in the third carcinoma, which extended in the subcutaneous tissue of the sole of the foot.

The more homogeneous the cancerous infiltration is in these cases, the more medullary the appearance of the nodule is on section. The few medullary cancers of the skin belong then preferentially to the small (and large) alveolar type; in the reticular and even the coarse reticular carcinomata there developes, in spite of the epithelial profusion, no true medullary, homogeneous appearance, for the firmly connected epithelial cords stand out independently and often contain concentric pearls.

Darier's case of sweat gland cancer has an appearance all its own, in which an extensive epithelial distribution in the subcutaneous tissue developed from the growth of the coil. Many epithelial cells lie singly or in twos and fours. But here and there, small, roundish or winding areas of six to ten epithelial cells have developed, which, especially in the deeper-lying, adipose tissue, possess the alveolar character. The cutis above the coil glands remains free from invasion. In this carcinoma the independence and mobility of the single epithelial cells is developed to a maximum. In certain places one can hardly believe that he is dealing with a uniform tumour.

Liquefaction and the formation of epithelial giant cells are rarer than in the large alveolar cancers. These secondary changes are evidently dependent on a sort of enclosure of the epithelial cells in closed cavities, which is rare in the small alveolar form. Mitoses, on the contrary, are as frequent in the small alveolar cancers as in the large. Cellular infiltration of the connective tissue is slight in both varieties; plasma and mast cells are only present in moderate number around.

IV.—Carcinomatous Lymphatic Infarctions.

I have already indicated this form of skin cancer as a sub-form, which usually indicates the origin of the cancer as lying outside the skin. Of four cases of my collection, which show this type, three were secondary to mammary cancer and only one was a primary cancer of the skin. The latter consequently deserves the more close consideration.

It was a reticular cancer, arising from the surface epithelium, which had developed in a scar. The epithelial processes hardly penetrate into the firm scar tissue which occupies the cutis, they

rather surround it laterally, and form, in the periphery of the whole scar, a cancerous infiltration of peculiar structure. Close to the margin of the scar this is more evident as the infiltration is less. One sees here, far apart, small, cylindrical epithelial processes, running on and between stretched, dense collagenous bundles, and giving off, on both sides (if they have room on all sides), almost perpendicular, short, lateral branches. Between these feathered epithelial processes there are found areas of firm scar tissue, quite free from cancer. Later on, the adjacent lateral branches everywhere run together, and there is developed a wide-meshed net of coarse epithelial processes, whose meshes are filled by a finer net of the finest epithelial reticulæ. The latter surround the individual, coarse connective tissue bundles of the periphery of the scar, without penetrating into its finer interstices. The more extended, thicker epithelial processes lie in the lymph vessels which accompany the main collagenous bundles of the periphery of the scar.

The cancerous infiltration thus represents a complete blocking of the lymph spaces and vessels of the scar, which are widened at the periphery. There is never found a rounding off of the epithelial processes into closed cancerous nests, as in the alveolar cancers, and accordingly no running together of the collagenous tissue. The firm connective tissue of the scar rather determines the direction of the epithelial stream, and forces it in the course of the pre-existing canals, which are accordingly infarcted by the cancerous tissue. Only in the adipose tissue, underneath the scar, do the small epithelial processes here and there again extend, and form, in the cavities of dissolved fat cells, small alveoli. Resistant as is the connective tissue of the scar, it yet shows itself devoid of reaction to the epithelial invasion. This causes only a very slight swelling of the connective tissue cells; no plasma and mast cells are developed. Possibly the poisonous products, which induce reaction, are directly removed by the affected lymphatics.

This case teaches us, that even the simple physical changes which accompany scar formation in the skin, suffice to confer on the epithelial masses a special mode of growth. One is inclined to assume, that, since the primary cancers of the skin do not usually follow in their invasion the lymph tracks, this must lie in the lesser power of resistance of the normal collagenous tissue, as opposed to the proliferating cancerous epithelium.

But it is notable enough that this same normal cutis tissue possesses this power of resistance to those cancers which come from some distance, from underlying organs (breast). One of my cases is a Paget's carcinoma, which, penetrating into the adipose tissue of the skin, has induced an irregular, coarse, cancerous reticulum, and, extending from

here, has permeated the cutis, outwards, with a fine lymph track infarct, which only here and there swells up to coarser reticulæ and nests. Here also the cutis remains largely passive to the invasion. A similar picture is presented by a "cancer en cuirasse" of the skin of the breast, whose periphery was composed of quite small, cancerous blocking of the lymph spaces of the cutis. An analogous cancerous infiltration of the skin of the breast (both these last preparations I owe to Dr Riehl) which, however, presented coarse cylindrical cancerous columns in the middle of the cutis, is surrounded by a dense collection of plasma cells.

As already indicated in the introduction, the preference of secondary cancers for the form of infarction indicates that they have a less deleterious action on the cutis tissue, and that, conversely, in the primary skin cancers, a still unknown, far-reaching, chemical agent causes a weakening of the collagenous framework. It cannot be the simple result of the cellular infiltration of the cutis, with its familiar, often collagen-destroying action, for cellular infiltration may, when a true cancerous destruction exists, be either present or absent; and we have just seen that even in cancerous infarctions, where it usually fails, it may be present, without at once paving the way into the cutis. On the other hand it is evident, that in primary cancer of the skin this power of resistance may be induced by secondary processes, such as scar formation.

As regards the nature of the epithelial cells, it is certainly not accidental that in all my cases they had a mucous membrane epithelial type, and were soft, plastic, almost cubical cells, without prickles, without epithelial threads, and without firm connection to each other.

The apparently so simple, though, considering the cancerous nature of the epithelium, natural form of the carcinomatous lymphatic infarctions of the skin, appears to be favoured by two factors, a special softness and plasticity of the epithelial cells on the one hand, and a special firmness of the collagenous framework on the other.

While, in the nature of the epithelial cells and the small form of the processes, the infarct approaches the small alveolar cancers, it is again like the reticular cancers, in the more or less evident net form in its whole formation. But this depends only on the net-formed anastomosis of the lymphatics, and not on the peculiar and wild onward growth of the epithelium, as in the true reticular and coarse reticular carcinomata. It is much more regular, and follows definite directions, which are parallel to the lines of cleavage of the affected part.

As, in describing the whole architecture of skin cancers, we have presented the most important forms, there only remains the description of the forms of degeneration, which will demonstrate certain striking

and interesting forms of cancer. But as above remarked, these can only lead to a *sub*-division of the cancers, since they are only present in a minority of the cases, which, moreover, always belong to one of the four chief groups described.

Hyalin degeneration of the epithelium is the most important change, not only on account of its frequent occurrence, but also because the hyalin products present resemblances to animal parasites, and have certainly occasionally been considered as such. Only a thorough knowledge of the hyalin metamorphosis in this tissue and all its products, will enable us definitely to recognise anything not belonging to it as foreign objects. On this ground I must particularly consider those criteria, which serve for the study of the metamorphosed elements, in particular, staining.

The completely hyalin degenerated epithelial cells are characterised, like all hyalin masses, by their homogeneous, shining, sometimes more waxy, sometimes more glassy, transparent character, their rounded form, and finally by their capacity for taking up only slightly most of the basic stains, while they take up the acid * stains greedily, and thus they are easily studied. Especially of value in this respect are acid fuchsin, eosin and orcein, since they stain the hyalin substance deeply, and, in addition, by their tone, supply very valuable contrasts to the best nuclear and protoplasmic stains. The details of the method will be better understood by the following description.

In order to get a rapid survey of the distribution and the forms of the hyalin material, inside the epithelial tissue, sections from a piece of tissue hardened in alcohol should be deeply stained in a one per cent. watery solution of acid fuchsin (a few hours up to a whole night). Then, to decolourize the protoplasm of the epithelium, the sections are placed for a short time in a one per cent. watery solution of picric acid, until they have taken a greyish yellow tinge, and then in a one per cent. spirituous solution of picric acid, where they are dehydrated, and where the hyalin pearls are evident, macroscopically, as light red points. They are then put through absolute alcohol and xylol and embedded in balsam.

With the high power the hyalin is seen in very varied forms. We soon learn to distinguish nine frequently occurring forms, which all show the same fuchsin red reaction. The first forms a section by itself; it comprises hyalin balls of different size, which lie free between the epithelial cells, and without connection with them, in the intercellular spaces. They are seldom single, usually in groups of four to ten individuals, lying closely together, are *absolutely round in form*, and

* In Ehrlich's sense, *i.e.* more or less neutral colour salts in which the colouring matter forms the acid.

have a diameter of 3-10μ; only rarely are they larger. The balls of one group are never all of the same size; they never show nuclear enclosures or any kind of processes. It is therefore just as little probable that they arise from leucocytes as from epithelial cells. They have the same significance as those hyalin balls which are found free in the lymphatic or vascular systems in almost all infectious processes. Possibly they arise from the hyalin degeneration of connective tissue cells and get into the epithelium from the lymph stream.

All other hyalin structures can be grouped together as of epithelial origin. This origin is indicated either by their position, inside the epithelial cell, in the cell substance or nuclear cavity, or by their continuity with epithelial cells through the prickle or thread apparatus of the latter. They may be divided into two chief groups of the *diffuse, unformed hyalin infiltration*, and the *formed, sharply defined hyalin structures.*

The diffuse hyalin infiltration of the epithelial cell is not very striking, as it is only evident in well-stained sections; but it is then seen that it is wider spread than the hyalin bodies are. Its importance lies, on the one hand, in the fact that it is often a preliminary stage in the formation of the latter, on the other, that here there can be no doubt of its epithelial origin. For here the epithelial cells themselves are partly or completely saturated with hyalin, without having lost their familiar structure and form. Complete diffuse infiltration of the epithelial cells is a rare appearance, since marked hyalin degeneration is usually accompanied by the solution of some part of the cell, and changes in its form. But the *limited, diffuse hyalin degeneration of the inner peri-nuclear substance of the cell body is extraordinarily common.* One often finds it developed, in different degrees, in all the cells in the neighbourhood of hyalin pearls. It indicates, even where no circumscribed hyalin bodies are found, the tendency to hyalin degeneration of the epithelium.

The other eight different kinds of structures of hyalin nature can be grouped together as formed epithelial derivatives. They appear—

1. In the form of *round balls* of considerable size (15-20μ), in the *interior of which* the more or less definite *remains of a nucleus* are evident, lying, in place of the nucleus, in the enlarged nuclear cavity, so that they are surrounded by a free space and that again by the diminished cell body, with its prickles.

2. Next to them come *irregular, long, much excavated, spirally twisted bodies, with more or less long processes, showing the same colour reaction,* which are all to be regarded as those of the first variety, to which concentric pressure and the force of growth has given an irregular, distorted form. The proof of this lies in the fact that, in

the thicker head of these bodies, sometimes even in the thinner processes, a cavity with nuclear or nucleoid contents is evident. They lie, like those of the first variety, but more or less bent and pressed together, in cavities, which are formed from the cell substance itself, the thinner end, the process, however, usually extends from the cell into an inter-cellular space, or directly into the cavity of a second cell, so that one or two cells are arranged like knobs on the ends of a long hyalin body.

3. From both of these forms there is clearly distinguished a third, somewhat *smaller* (7 - 15μ), likewise round, which also lies in *the nuclear cavities*, but *close to the nucleus, and itself containing no nucleoid material.* These bodies are more homogeneous than those described under 1 and 2.

4. These smaller anuclear bodies also often appear *elongated* as if provided with a *handle*, and this handle often reaches out of the cell and may eventually reach a second nuclear cavity. The colour reaction of the handle is exactly the same as that of the round bodies.

5. In addition to the processes and handles of the nuclear and anuclear hyalin bodies, there are, further, similar structures, which are not connected with any bodies, but, as *hyalin rods* or winding loops of *finer* or *thicker tendrils*, run between the epithelial cells. Their breadth varies from 2-5μ, their length from 10-30μ. They usually pass at both ends into the body or mantle substance of a cell which is not hyalin.

6. The next two forms are *capsulated structures.* There is seen a *well-preserved nucleus, or several, lying in a hyalin degenerated vesicular, or, on section, ring-formed cell*, which, by a few retained prickles and threads of connection with the neighbouring cells, is still recognisable. Sometimes the hyalin vesicle is detached from the neighbouring cells, is smooth, inflated, and its walls thinned; it then usually contains, between the nucleus and the hyalin shell, an unstained mass.

7. A second form of flake or vesicle-like hyalin bodies with nuclear cavities shows handle-like processes, exactly analogous to those first described of the intra-cellular hyalin bodies.

8. A third form of the *hyalin vesicle* contains, instead of the nucleus, a *granular spherical body exactly resembling type* 1. Then the nuclear remains are concentrically enclosed by *two hyalin capsules*, which are separated from one another by a narrower or broader space.

In a last group of forms, one can unite all of those individually very different *conglomerations*, which have arisen from the compression and coalescence of the individual elements into hyalin pearls. The more

loosely arranged and also the marginal parts of the older, firmer pearls frequently allow one to recognise, very clearly, the formation from the previously described forms. Where, on the contrary, firmer concentric pressure has pressed the bodies closer and closer together, there the fuchsin stain no longer shows the exact seat of the hyalin substance, since all the enclosed compressed bodies take the stain. With this stain a few other substances take a red tinge, the horny layer and the nucleoli, and in a lesser degree those parts of the epithelial cells, showing the commencement of the hyalin degeneration. The latter circumstance, together with the brilliantly sharp prominence of the yellow stained epithelial threads, makes this method especially valuable in determining those parts in which the degeneration begins, while, on the other hand, the simultaneous staining of the nucleoli interferes with a close observation of the degenerative processes in the nucleus. It is now evident, as remarked above, that in many single epithelial cells, which lie scattered in the neighbourhood of the pearls, the internal threads lying next the nucleus—I will call them shortly endofibrillation—have partly or completely taken up the red stain, while the external threads (ectofibrillation), which pass into the prickles, are pure yellow. But we recognise definitely the individual threads of the endofibrillation; the red colour adheres to the substance surrounding them. The more the fibrillation in this part of the cell disappears, the more light red is it. It appears as if the epithelial threads were simply embedded in an interstitial substance, swollen up with hyalin, and thickened. A series of facts become thus comprehensible. The nucleated, round and elongated hyalin balls (types 1 and 2) consist of the endofibrillation of affected epithelial cells, which has become hyalin and still encloses remains of the nucleus. Just as the internal filaments normally surround the nucleus in loops, and, running through the cell substance, pass into the threads of neighbouring cells (Cajal, Kromayer), so here the hyalin vesicles and rings extend in handle-like elongations, which penetrate the cell wall, and, like bridges, unite neighbouring cells. The relative independence of the internal fibrillation, and its connection with the threads of neighbouring cells, enable us to understand how the inner part of the cell, containing the nucleus, separates itself from the outer cell substance, and in places sends processes through it. *The hyalin degeneration does not extend from cell to cell, but along the thread system of the epithelial cells*, therefore producing hyalin parts of cells, which pass into cell bridges. Thus the presence of long hyalin rafters and cords is explained. They are the elongated connecting bridges of cells, otherwise separated, parts of the ecto threads, which have degenerated. One sees them passing at both ends into the external fibrillation of well-preserved epithelial cells.

It is more difficult to explain the small hyalin balls without nuclei, which lie beside the well-preserved nuclei, and often show handle-like processes. Certainly, protoplasmic threads are often evident in them, so that it appears plausible to ascribe them to those cells, in which only a part of the inner fibrillation has become hyalin, and has separated itself from the remainder of the cell body. But on account of the absence of nuclear enclosures the genesis is by no means so clear. But it is evident if we stain the internal fibrillation very deeply, and take care to preserve the hyalin stain, in addition, with acid colours. Since, for the first purpose, gentian violet, iodine, iodide of potassium, and anilin are necessary, a series of basic fluids, one must regretfully abandon acid fuchsin for the second purpose. Eosin is less sensitive to basic contrast stains; the sections are overstained for a night in 1 per cent. watery solution of eosin, and then treated, in the ordinary way, on the slide, with the solution of gentian violet, iodine, and anilin oil, until they are completely cleared up. Although the epithelial threads, in general, are only faintly stained, the large epithelial cells lying around the pearls show the internal fibrillation very clearly. By comparing adjacent sections of a series, it is evident that it is those large epithelial cells, which, with the fuchsin picric method, show the commencement of hyalin degeneration between the internal fibrillation, which here, with the eosin gentian method, show the latter with great distinctness. Where there, then, are found complete, fuchsin-red hyalin rings (vesicles) enclosing a nucleus, there are found here paler eosin-red rings, permeated by dark blue, internal fibrils, and also enclosing a nucleus. But further, it is evident that the anuclear, fuchsin-red clumps of that method are here replaced by deep-blue stained, internal fibrils, which, surrounded by hyalin substance and compressed into a tangle, occupy a part, often the half or more of the nuclear cavity. Near it lies the well-preserved (amitotically divided) epithelial nucleus or nuclei (2-8). It looks as if the loop of the internal fibrillation had been drawn on, had allowed the nuclei to escape, and now lay, tangled, in a corner of the old nuclear cavity. And this all the more, as most anuclear hyalin clumps appear pedunculated with this stain, and, in the hyalin handle, the blue stained internal fibres, penetrating the outer substance of the cell, which reach to neighbouring cells, become visible.

The anuclear hyalin clumps are, like those containing nuclear enclosures, hyalin degenerated parts of the internal fibrillation loosened from the bodies of the epithelial cells, and their processes and handles are the hyalin degenerated internal fibres, emerging and extending to other cells.

The forms described under 6, 7, and 8, are also capable of a simple

explanation. If—as is apparently rarely the case—the external fibrillation of a cell alone degenerates, there developes a voluminous hyalin vesicle or a ring, which sometimes carries, on its outer surface, remains of degenerated prickles, now and again extending into a hyalin cord, which leads, like a bridge, to another cell. If the external fibrillation is chiefly swollen and hyalin we have form 6; if, on the other hand, the endofibrillation also undergoes hyalin degeneration, form 8 developes, which shows an external, large vesicle, and a small inner one with nuclei, or a simple, large, hyalin vesicle with nuclei, along with a hyalin, solid knob inside. In place of two relatively independent, enclosed vesicles, there is seen, now and again, an incompletely hyalin degenerated cell, with the nucleus still visible; thus a very simple form, but not so frequent as one would expect. The remarkable, flourished, complicated forms of hyalin epithelial metamorphosis are due to the fact, that the latter attacks the cells less as individuals than as different parts of all the cells of a common system of fibres. The still more complicated forms of smaller and larger hyalin pearls require no further explanation, for they represent conglomerations of the hyalin elements, already described, which have still further degenerated, from centripetal pressure and tangential traction. Even the very peculiar jelly-fish-like pearls, with white radial processes, are explainable from the elementary forms. But the relations of the nucleus deserve a few words.

From what has been said, it appears as if the nuclei were always merely passive enclosures in the hyalin. But to determine the fact that the nuclei do not undergo the same degeneration, we require a stain which permits of a better distinction between nuclear substance and hyalin matter, than acid fuchsin and eosin. For this, orcein may be recommended. With prolonged staining it colours hyalin matter brownish-red, and shows no special reaction to the nuclei and nucleoli. It is best to stain the sections previously in water-blue, and then in weak, neutral spirituous orcein solution for a whole night. The orcein colour then replaces the blue in the protoplasm of the epithelium, and the epithelial fibrillation stands out clearly in the hyalin, in the nuclear juice, and in the nuclear membrane, but not in the nucleoli nor in the horny substance, so that these stand out blue. We note with this stain, that all nuclear enclosures in the hyalin vesicles and rings also retain their blue colour and do not take on the orcein stain of hyalin. Indeed, the blue spots in the centre of the hyalin clump are, some of them, very much enlarged. As the enclosed nucleus shrinks, the nucleolus almost always swells up until it almost entirely fills the diminished nuclear cavity. Even in very old, compressed, dark brown, hyalin clumps we frequently note, in the middle of the pearl, a blue centre. Finally, this is no longer recognisable, but whether this points

to a secondary hyalin transformation of the remains of the nucleus, or only to an increased difficulty in the penetration of the colour, must be left undecided.

At all events, so much is certain from the water blue orcein preparations,* that the epithelial nuclei do not primarily undergo hyalin metamorphosis, and, if at all, are only attacked with difficulty.

If we look back at these different forms of epithelial hyalin, we must admit that some of them, especially the hyalin vesicles with nuclear enclosures, those with hyalin clumps along with the nuclei, and the hyalin vesicles with double walls, are not unlike certain animal protozoa, in a stage of encapsulation. But if anyone will convince himself of the simple degenerative nature of these forms, he has only to use the stains, here described, on appropriate carcinomata, and especially to note the extension of the hyalin along the epithelial fibres.

For the study of hyalin degeneration, two fungating cancers were of especial use to me, a papillary one, which developed on the base of "sailor's skin," and a coarse reticular, ordinary cancer of the face. Both showed the forms of degeneration described, in abundance.

The cornification of cancerous tissue is a simpler process than that of hyalin degeneration, although it also is by no means clear. At first it appears self-evident, that an epithelial tissue, formed from the prickle layer, should show the tendency to cornification, which is normally shown on the surface, even in the depths of the cancerous tissue. It appears natural that the change of direction of the mitosis, in general, would frequently lead to a crossing of the direction of growth, and consequently to the formation of the ultimate products of cornification, in the centre of the epithelial processes, which would supply the nucleus of future horny pearls. But two very readily observed facts contradict such a simple explanation, namely: first, the absence of horny pearls in other dermatoses, accompanied by a-typical epithelial growth, and then the circumstance that all cancers of the skin do not show horny pearls, which would be the case if the above explanation were correct. But the pearly cancers cannot be called frequent. Of my seventy cases there were only eight which showed horny pearls; of these, in only three were they present in abundance. There must then be another factor which induces their formation. If we consider them more closely, we see that most of them (6) are fungating cancers of the lip, which show, in superficial parts, broad, centrally cornified, epithelial taps, and in their deeper parts a moderate epithelial net, in which horny pearls, of different size, lie isolated and scattered. We can hardly regard the latter as detached parts of horny centres, which have penetrated from without. Firstly, no connection is evident, and further,

* In this the kerato-hyalin is stained blue, not taking the orcein stain, one of the many stains of this substance, which distinguishes it from other hyalin substances.

the horny penetrations show all the distinctions of ordinary horny layer; a much enlarged granular layer at the base of the depresssion, and a distinctly separable, basal horny layer, while these distinctions are absent in the isolated pearls. Were these simply snared off from the penetrations, they would frequently show traces of transitional cells around them.

The horny pearls follow a principle of cornification of their own. In the middle of the prickle layer of the cancerous processes, the epithelium is arranged concentrically, around a common centre. The cells become extraordinarily long and small. The nucleus usually persists, shrunken, the protoplasm becomes pale, the epithelial fibrillation indistinct, and the whole cell is cloudy and stains badly, so that the circumference of a horny pearl is usually striking in its transparency. Very often, but not invariably, usually in the larger horny pearls, these concentrically arranged epithelial cells contain a moderate number of fine kerato-hyalin granules. This corresponds with the well-known fact, that the granular layer is reduced to nothing, or to a very slight remnant, both by compression and by excessive moisture. Here, of course, only radial compression has to be considered. Following this layer of clear, enlarged cells, is the horny pearl proper, consisting of thin, compressed, homogeneous, partly anuclear cell bodies, which are rolled inside each other like the scales of an onion, and already show the horny reaction with appropriate staining, *i.e.*, saturated straw-yellow colour with picro-carmin and picro-cochineal, and blue, with water-blue orcein. With the orcein stain, we note that, in several of the horny pearls an innermost nucleus stands out from the mass of the horny pearl. Since it is hardly possible that an unaltered prickle cell can have persisted inside this compressed mass, and taken the orcein stain, it is probable that this inmost part of the pearl consists of a hyalin degenerated cell, especially as it has the form of a rounded or spirally twisted clump, which stains deep brownish violet, like old hyalin.

The probability, that hyalin degenerated, epithelial cells form the nucleus of a part of the horny pearl, is supported by the fact, that, on thorough search in these same epithelial processes, where the horny pearls are present, a few hyalin degenerated epithelial cells are by no means rare, and is finally certified by the observation that, around such isolated hyalin clumps, the immediately adjacent epithelium is concentrically arranged and commencing to flatten. This then would explain the presence of horny pearls in the depths of the epithelium, and I would regard it as not improbable, that all horny pearls owe their origin to some such foreign, firm nucleus. But I can, as yet, only maintain this genesis for some of the horny pearls. It is not impossible that an epithelial cell, prematurely cornified, from some

unknown cause, might form the foundation stone of other horny pearls, but I would regard the presence of such isolated, true cornification of individual epithelial cells, far from the surface, as very improbable, while the isolated hyalin metamorphosis of the cell is a very wide-spread, common process.

Thus the keratinisation of carcinoma is probably only a special result of the hyalin metamorphosis, in those cases where the tendency to wide-spread hyalin degeneration is absent, where, on the contrary, a certain dryness of the epithelium and other conditions concerned in true cornification are present, which make the individual hyalin cells the foundation stone of an incomplete deep cornification. This necessary conjunction of favouring circumstances would then explain the relatively rare occurrence of horny pearls in cutaneous cancer.

The *liquefactions* of carcinomatous tissue are very different in their nature. We have mainly to distinguish two different processes, which are only exceptionally combined—namely, the *liquefaction of the epithelial tissue* and the *colloid degeneration of the connective tissue.* It is especially important to be familiar with the latter, because many apparent epithelial colliquations prove, on more careful examination, to be mucoid alterations of the stroma.

Epithelial liquefaction either leads to small, isolated cavities, or to larger connected cavities and canals. The former play an important rôle inside the prickle layer of the surface, in a particular form of carcinoma—namely, Paget's disease of the nipple. It is fully described under that heading. But it is also found in cylindrical cancers, deep down in the skin. Of this occurrence, I have only *one* distinct case. It is a true cylindrical cancer of the coil glands, which I owe to Dr Riehl, which has taken on a tubular structure, mainly from the wide-spread, central liquefaction. In other places, a few central cells are liquefied, and there develope small, isolated cavities, which partly communicate with one another. This is possibly the commencement of the central liquefaction of the whole epithelial cord. In this liquefaction the nuclei also perish, and so few remnants of cells are seen in the cavities, that one can hardly help thinking that he is dealing, not with a formation of vesicles, but with a sort of cellular secretion, which the derivatives of coil gland epithelium might quite well provide. The extensive, tubular liquefaction of many epithelial processes in these cancers, supplies a good example of tubular carcinoma. The cavity formation does not directly depend on the lumen of the coil glands, but these grow first into thick, branched processes, which then undergo central liquefaction, and thus the previously cubical cells give place to a single or double marginal layer of cylindrical oblique ones. Here also there are few cellular remains to be

seen in the lumen of the new formed canals, although these by no means open free on the surface. The whole tumour forms a solid nodule, elevated over the skin, and presenting a radial formation, in that the isolated cancerous cylinders, proceeding from the coil glands, grow outwards between the normal follicles of the skin, and passively distend the surface between the follicles, without rupturing it.

More remarkable than this development of a tubular cancer, partially clothed with cylinder cells from the coil glands, is the existence of a cylindrical celled cancer of the perinæum, which arose directly from surface epithelium. I owe it to Dr E. Fraenkel. The epidermic ridges have here grown, in many places, into pretty large, conical taps, which, by increasing cornification and the falling out of the horny layer, excavate cavities, not unlike the infundibulum of a hair follicle. In the depth of this infundibulum there takes place somewhat suddenly the remarkable metaplasia of ordinary cubical surface epithelium, into pretty high and small cylindrical epithelium, and the processes and cylinders, in their extension, retain this form and the tendency to form a central cavity. The whole new growth at first gives the impression of a tubular adenoma. But one has only to reflect that such broad, cylindrical, epithelium-lined glands are not present in the skin, that the loops grow through the skin very irregularly and show themselves to be processes excavated from the surface, and the diagnosis of tubular cancer cannot be avoided. Further, between the epithelial processes, there are large areas of plasma cells, and a good many mast cells complete the cancerous type. Certainly this case of metaplasia of the surface epithelium may be unique.

There is, in distinction to this formation of cavities without firm contents, a series of other cases, in which there is no total central liquefaction, but only partial solution of a few cells, whereby the other cells are loosened, isolated, and converted into cellular debris. A cancer of the knee, one of the penis, and a Paget's cancer showed this transformation of broad epithelial processes into cystoid, tubular spaces, filled with epithelial debris. Usually an epithelial rim, adjacent to the connective tissue, is well preserved. Then follow deformed cells, and debris, separated by spaces. And then, in the centre, there swim a few epithelial cells and collections of them, which, freed from the pressure of the others, have taken a spherical form, and often show swelling and homogenisation of the protoplasm, with a well-preserved nucleus. Sometimes the latter is undergoing mitosis. In other cases it is only very faintly stained; in process of solution. Many cells are œdematous, distended and partly liquefied, free nuclei are also found. In still other cells the thickening of the ectoplasm has extended, while the nuclear space has dilated, so that one may speak of ballooning de-

generation. Other cells, again, have undergone hyalin degeneration, and completely hyalin pearls are found enclosed in the epithelial debris. The fate of the latter is, only exceptionally, simple absorption. Where outward rupture does not take place, there is probably absorption of the liquid, and calcification of the dried up epithelial debris. In many parts of this carcinoma there were certainly found larger spaces, completely filled with fluid and fibrinous threads, partly enclosed by epithelium. But I do not believe that this was true epithelial liquefaction, but rather the extension of mucoid, degenerated connective tissue between the epithelial processes, which led to a slow but complete absorption of the latter.

This I was able to confirm from a coarse reticular, deep Rodent ulcer. Here the broad epithelial processes were permeated by a large number of circular spaces, which were striking even with a low power, and with ordinary methyl-blue stain took a reddish tinge (reaction of mucin). Since these mostly appear in the centre of the epithelial processes, it was tempting to regard them as liquefied epithelial cells. But there was not the slightest trace of epithelium. Then it was further seen, that some of these marginal spaces were connected with very small connective tissue processes, in the compact epithelium. A special stain for connective tissue fibres (acid fuchsin, picric acid) now showed, that the apparently compact epithelial masses were penetrated by a great number of isolated connective tissue fibres, and that these partly reappeared in the mucinous spaces. The isolated spaces in the epithelium may then very well owe their origin to a mucous degeneration of the connective tissue. The actively growing, cancerous epithelium encloses more fragments of collagenous tissue than one would suspect, without specific staining.

As this mucous softening of the stroma extends, the adjacent epithelium gradually falls a victim to it. The cells liquefy, singly or in series, and one always sees, at the extending margin, a-nuclear, faintly-stained, fragmentary epithelial cells, enclosed in a gelatinous connecting substance. If there is, in addition, as in a cancer of the penis, a simultaneous central epithelial liquefaction, it is by no means easy to draw a line between the two layers.

The glandular cancers of the skin are especially liable to this mucoid transformation of the surrounding connective tissue. I have before me, of these rare tumours, a coil gland, and a sebaceous gland cancer, both from the orifice of the nose; both show a colloid degeneration of the connective tissue, leading to running together and isolation of the cancerous epithelium. The former extends as a tubular cancer in the subcutaneous tissue. The degeneration of the connective tissue is very great; it leads to isolation of individual, cloudy, cancerous

elements, and evidently opposes considerable resistance to the unlimited extension of the cancer.

The sebaceous gland cancer is the only one in my collection, which can, with certainty, so be named. It is not only acinous in form, but evidently proceeds from the sebaceous glands of a small wart, some of which are still well preserved, and not from the surface epithelium. In addition to the sebaceous glands, there are, in this case, no other epithelial structures deep down. The cancerous acini are separated by the swelling mucoid stroma; the individual cancer cells are isolated and tend to liquefy. The whole degenerated part takes, with methyl-blue stain, a reddish colour, so that the blue epithelium is very clearly marked off from the red, colloid connective tissue. In both cancers the absence of cellular infiltration, and especially of mast cells, is striking.

2. *Carcinoma Jacob, True Rodent Ulcer.*

This form of cancer shows, in its very prolonged course, two very distinct stages; that of year-long duration, which usually comes under the dermatologist or ophthalmologist, and the later one which comes under the surgeon. In it the new formation is only present in miniature, and is as nothing, compared to the extraordinarily slowly-advancing ulceration.

The cancer begins as a rosy-red or often pearly-grey, smooth nodule, the size of a mustard seed, which reaches about one millimetre over the surrounding level, and extends very slowly, while it sinks in in the centre. Thus there develope greyish-yellow or greyish-red, smooth, oval spots, the size of a pea to a shilling, lying on, or slightly beneath the level of the healthy skin, which are surrounded by a very characteristic, fine, now and again rolled, mother-of-pearl, ridge-like border, from which small, nodular thickenings often extend. Now and then, fine, venous ramifications extend over the border and the centre, and there is occasionally slight pigmentation. The natural lines of the skin are always diminished or absent at these spots, which are striking from their smoothness and their marginal shimmer. There is no distinct thickening of the skin and no peripheral inflammation. Even at this stage, very slight traumata suffice to remove the horny layer, usually in the centre, and there is formed a dark crust of bloody serum and young horny layer. Left to itself, this falls off, and thus the affection gets its premature scar-like appearance. Repeated casting of the horny layer finally leads to persistent ulceration, and thus commences the second, ulcerative stage.

The ulceration extends at first only to the original border, which also loses its horny layer, so that the bright red, apparently smooth surface of the ulcer, lying at the level of the healthy tissue, is surrounded by a sharp, finely-excavated, strikingly indifferent border, neither undermined, projecting, nor reddened. An elevated ridge as the margin of the ulcer, only exists where remains of the first stage are present. Later, the ulcer extends very, very slowly, as such. The appearance of the surface is always bright red or yellowish red, resembling healthy granulation, with very little laudable, serous discharge. It only rarely bleeds and causes very little pain.

This form of cancer is invariably limited to the region of the eye. Most frequently it affects the eyelid, and a ring, two to three centimetres broad, around, on the forehead, temples and cheeks. Later appearing spots are limited to a region, which comprises the upper two-thirds of the face, and is margined by the hairy borders of the forehead, the ears, and a line drawn from the lobule of the ear to the mouth. Jacob's carcinoma, appearing outside this region, should only be diagnosed with the greatest caution, and when all the other symptoms agree. Such cases are almost always superficial cancers of other genesis.

As the ulceration extends, it usually affects the orbit, destroying the eye, then the malar bones and upper jaw; finally the cancer penetrates the skull. This may take forty years and more. The ulceration always retains its benignant character: a fresh colour, a pretty smooth, though later, excavated surface, a trivial, laudable discharge, and only slight pain and hæmorrhage. The lymph glands never swell; there is never metastasis and no cachexia. Death is due to the local destruction of vital organs, or hæmorrhage.

The histological investigation of rodent ulcer must first explain the striking clinical symptoms of the first stage: the flat form, the peripheral ridge, the primary nodule, and then the remarkable indolence and dryness of the ulcerated surface in the second stage. We may say, that not only do the histological appearances exactly correspond to the clinical ones, but are so characteristic, that it cannot be readily confused with any other form of cancer. But I cannot sufficiently reiterate, that this description only relates to true Jacob's ulcer, and is of no value, if, as so often happens in Germany, every flat, superficial cancerous ulcer is called Rodent ulcer. For this reason I have described the exact clinical symptoms of the cancer, to which alone the following description refers.

Of true rodent ulcers, I have six from the eye (four of them kindly given me by Dr Brooke), and two from the cheek. I may at once note, that the formation of this cancer is only influenced by its seat on the eyelid, in so far as a specific conjunctival disease is invariably present. Otherwise it behaves so similarly in all cases, that a common description suffices for all. The first stage is represented by all the ulcers of the eye, the last, especially by an ulcer from the cheek, which had covered the whole left half of the face, while, from the last rodent ulcer, preparations of both stages were got. This has so far a special interest, since it developed at the right angle of the mouth of an old gentleman, the lowest margin of the rodent ulcer region, and from here affected the right cheek and the upper lip, so that a V-shaped excision was necessary (a very rare occurrence in Jacob's ulcer). But the diagnosis was absolutely certain, from the typical presence of all the other symptoms, during years of observation.

The primary, smooth, mother-of-pearl-like nodule, and the nodules appearing on the peripheral border in the first stage, have the same

structure. There is a very circumscribed thickening of the prickle layer, which only elevates and smoothes the very little thickened horny layer, and a slight downward extension of a few cylindrical epithelial processes. These are usually connected with the epidermis by a small neck, then widen a little, usually wind laterally or round one another and terminate in the middle of the cutis. They are surrounded — like the primary affection of the epithelium in Paget's carcinoma—by a strikingly broad wall of plasmoma, and a few areas of plasma cells are seen under the healthy epidermis beyond. Most important, however, is a change of the inter-epithelial connective tissue, which is present in many cylindrical cancers, but especially in the styloid. In it there are only few plasma cells, but rather more mast cells. Not only are the spindle cells swollen and multiplied; there commences a new formation of fibrillary tissue.

The changes of the connective tissue, between the epithelial processes, are more evident, when the nodule has flattened and extended peripherally. Then the slight thickening of the prickle layer extends concentrically, as a mother-of-pearl ridge, and with it the peripheral border of plasmomatic infiltration. But in the centre, where the depression takes place, the proliferation on the surface disappears, and the prickle layer is thinned; the epithelial processes also become thinned, but extend further into the cutis, which is converted, by new formation of spindle cells and collagenous tissue, into a very firm, fibrous, scirrhous, elastin-free tissue, whose fibres are arranged differently from the original tissue of the cutis. Under this, again, we find plasma cells, which form a shell-like, thin margin from the healthy tissue.

Further extension takes place by the cylindrical processes extending very slowly into the thickened connective tissue, where they twist and wind in the most complicated manner. Where their advance is arrested, they swell up somewhat, and send off lateral processes, which give to the tumour a somewhat reticular character.

But there are two conditions always preserved in the extension of the process; on the one hand, the growth always remains flat, it never elevates itself, like other cancers, over the level of the healthy skin; and, on the other hand, the epithelial processes preserve their small form, and their relatively wide separation by firm connective tissue. This latter point must be a necessary correlation, for however far Rodent ulcer extends its thin processes, it is always surrounded by an abnormally dense, pathologically altered cutis. Thus the relative paucity of epithelial cells, as well as of connective tissue new growth, leads to the absence of a definite tumour.

But there is a third point, which is an important character of this form of cancer, and enables one to distinguish it, at the first glance,

from other cylindrical carcinomata. That is the almost constant displacement of the cells, inside the processes; this also must be ascribed to the abnormal density of the connective tissue around. Not only are the central cells in the processes elongated, but they are spindle and rod-shaped. The peripheral cells are also very exceptionally cubical, never cylindrical, but mostly also spindle-shaped, and therefore placed obliquely, as if spiral traction or pressure had been exerted on the whole epithelial process. Often the epithelial processes terminate in a point, with such obliquely arranged, rod and spindle-shaped epithelium, and end free in the tissue. All show concave depressions, in which convex distensions of the stroma lie, thus showing that the compressed form of the cylinders is to be ascribed to the abnormally great pressure of the stroma.

Thus, in this stage of apparent scarring, the new growth forms a fibrinous plate, occupying the upper half of the cutis, in which there run thin, pointed processes of epithelium, derived from the surface.

This latter may be preserved thinned, or may be sometimes thrown off, without necrotic changes attacking the surface. Towards the healthy cutis, the cancer is margined by a shell of plasmoma, which is succeeded by scattered areas of plasma cells.

If long undisturbed, as is usually the case on the eyelid, the cancer gradually becomes somewhat swollen and elevated. But the under margin of the cutis remains the same. Inside the cancerous plate the thin epithelial processes are ever increasing, and distend the plate, without completely running together, so that such nodules require very good staining, in order to determine the margin between epithelium and connective tissue. In such older cancers of the lid, which however still belong to the first stage, the plasma cell infiltration usually extends widely beyond the border of the lid, both on the healthy skin and under the mucous membrane. On the latter it is constant, so that rodent ulcer of the border of the lid is always accompanied by marked reddening and swelling of the conjunctiva. In such places the conjunctival epithelium is often surrounded by a broad layer of plasma cells, often broader and more cellular than that round the rodent ulcer itself. One is almost compelled to regard the conjunctival epithelium as also diseased, although it sends no cancerous processes into the skin of the lid. At anyrate, the conjunctival epithelium in the neighbourhood of the Rodent ulcer is swollen; its depressions have enlarged, and contain a large number of clear, vacuolated spaces. Possibly it contains and produces the cancer poison, but is itself prevented from proliferating by the wall of plasmoma; the spaces in the epithelium, and the broad plasmoma area beneath, recall the "eczematous" stage of Paget's cancer.

We find the commencement of the second stage, on the rodent ulcer of the lip. Here the cancerous infiltration is only four to six millimetres broad, although its under surface is ten to twenty millimetres below the level of the skin around. The additional six millimetres are accounted for by the smooth, round loss of sub-

FIG. 26.—Rodent ulcer of the eyelid.

The left lower corner shows the skin unaffected. Then follows the "ulcer," consisting of the epithelial processes in a scirrhous cutis. On the right the conjunctival membrane *M M.*, with the plasmomatic infiltration *T.* beneath it. The cilia have fallen out.

stance, the ulcer. The whole new growth has only sunk down, gaining as much ground on the under surface as it loses above by gradual exfoliation. Even in its finer details, the new growth is the same as the old; small epithelial cylinders run through a young, fibrous tissue, containing spindle cells and small areas of plasma cells, and this double new growth is surrounded by a dense halo of plasma cells, with scattered mast cells. The ingrowth of the connective tissue

and epithelial new growth may be very clearly followed here, for it is not in ordinary subcutaneous tissue, but in the substance of the orbicularis muscle, and thus the individual muscular bundles are surrounded, and undergo pressure atrophy.*

The nature of the loss of substance in this slow ulceration is also remarkable. In many places it appears as if the old epidermis still clothed the ulcer. There is found a broad prickle layer, with epithelial processes which lose themselves in the cancerous ones. But usually the latter end abruptly on the surface, and even the intermediate fibrous new formation ends suddenly, without any particular zone of degeneration, or line of demarcation. Only the outermost epithelial cells and connective tissue parts are dried up and perish, if previous caustics have not produced a scab. On the one hand, it is clear, that a true, although almost insensible ulceration has taken place, and that the ulcer does not represent a simple depression of the surface. But, on the other hand, the very normal-looking islands of surface epithelium, in the depths of the ulcer, show that they can very easily be skinned over by the cancerous processes from the neighbourhood. The resistance of the connective tissue, as well as the tendency to skinning over, fully explains the indolence, the long duration, and the resistance of such ulcers. It also explains, further, why, in spite of rapid epithelial loss from the surface, there is, in many cases, no deepening and no excavation of the ulcer, so that there is a tendency to regard these open cancers as healthy, granulating surfaces, as we know Paget did, when he found no cancerous processes in the ulceration.

To this representation of the commencement of the second stage, I can contrast a series from the last stage of the whole affection, in which, only at the last, the special character of Rodent ulcer disappears, and the cancer resembles other ingrowing cancers. It loses its scirrhous character, and assumes a more medullary type. As we might very well expect, this does not occur unless grave metamorphosis of the stroma occur simultaneously or precede it. At first the collagenous substance and a number of the spindle cells disappear, while the few nests of plasma cells remain. At the same time the lymph spaces enlarge, and the whole connective tissue assumes a more succulent character. Consequently the proliferating epithelial processes extend; they retain the cylindrical form, but become excessively broad, often spherically swollen, and run together to form a coarse epithelial net. It is remarkable, that in this more luxuriant epithelial folding, the staining capability of the individual cells remains the same; the epithelial processes are rather more difficult to stain, and poorer in chromo-

* In another of my cancers of the lip the muscular substance broke down into hyalin fragments.

philic protoplasm than the small styloid cylinders of the first stage. But further, there appear in the swollen processes, connected spaces, in which appropriate staining shows a few collagenous fibres, and which, in describing epithelial liquefaction (see carcinoma vulgare), we have learned to recognise as pre-existing, œdematous, swollen remains of connective tissue, around which the epithelial cells also undergo slow colliquation. Thus the epithelial processes, along with the marginal connective tissue, are excavated, collapse, and large parts of the new formation disappear. On the other hand, we understand that the growth of the epithelium, deep down, can now be more rapid, for the new formation of fibrous tissue, which at the commencement limited the cancerous growth, has gone, and an œdematous connective tissue taken its place. Then comes invasion of the bones of the face, and ultimately death.

3. *Carcinoma of the Sailor's skin.*

Under the name "sailor's skin," I have described an affection of those parts of the skin exposed to the weather, which I have chiefly observed in those spending their lives at sea. At first there appears on the ears, the adjacent parts of the cheeks and temples, the backs of the hands and fingers, a diffuse cyanotic redness, similar to that due to frost. Then the skin becomes mottled, spots of pigment, sometimes reticulated, becoming evident. The islands of skin between them partly lose their pigment. At the same time the skin becomes rough and hard, by thickening of the horny layer, and in some places almost callous or warty. On stroking the skin we can *feel* scarcely visible, horny processes.

To this first stage of erythema, pigmentation and hyperkeratosis, which may last for years, there succeeds a further one, in which large, warty-like growths, hypertrophies of the sebaceous glands, and papillary and ulcerating carcinomata appear. Usually all these forms of growth are found together at this period. The ulcers all have an indolent, slow, and superficially "rodent" character (like Jacob's ulcer), but they begin with a warty nodule.

This dermatosis is of great importance in the genesis of cancer of the skin in general, since it presents a form of carcinoma as the last stage of a series of cancer-like, but innocent growths. From a case, six years under observation, I have pretty well all the modifications of the epidermic changes, which may be observed succeeding or accompanying each other. In general, one gets the impression, that clinical observation is so far deceptive, for the deep histological changes do not usually correspond to the externally visible appearances.

The slightest degree of epidermic change is seen in sections, which show the whole ridge system of the epidermis equally thickened, and the papillæ correspondingly thinned. Sometimes the ridges run together to a broad plate, from which most of the papillæ have retracted. The granular layer is regularly widened, as is the horny

layer, which, here and there, shows distinct nuclear remains. With a higher power we see still greater departures from the normal. There are found, in all parts of the prickle layer, otherwise well preserved epithelial cells, with two, three, four or six nuclei, lying packed together in a nuclear cavity. The body of these cells is usually enlarged, but the connection with neighbouring cells is not destroyed. In other places, individual cells are partly or completely converted into hyalin fragments, with or without nuclear remains. Both around these fragments and around the multi-nuclear epithelial cells, immediately adjacent epithelial cells are often concentrically grouped, so that the arrangement of the prickle layer, as a whole, is here and there irregular. At this stage the changes in the connective tissue are very slight, and are limited to an excessive number of mast cells, a slight multiplication of the spindle cells in the papillary body, and a dilatation of the capillaries. A brown granular pigment is present, so far as I see, irregularly, and not in the neighbourhood of the vessels, but only at the epithelial border, and in and between the basal prickle cells, especially at the under angles of the ridges.

From this earliest stage, which is clinically evident as a callous thickening of the surface, the development proceeds in two divergent directions, according as hyperkeratosis or acanthosis is more pronounced. The simpler appearances follow the former; they lead to forms which resemble callosities, corns, and hard warts. Such a piece of skin shows the growth of the prickle layer advanced, so that, by the persistence of some papillæ, an irregular formation of the papillary body, with very small and very large, simple and secondary papillæ, developes. The horny layer is still more altered. In most places it is only considerably thickened, but still shows, like the broad granular layer beneath, its normal formation.

But in many places it extends into the depths of the broad ridges, and forms conical horny taps, like corns. On these places the granular layer is usually thinned or has disappeared, and the horny cells are nucleated. The whole horny tap usually reaches over the adjacent horny layer in a blunt point. If longer papillæ margin the epithelial ridges around the horny tap, the thick horny layer over their apices is softened, undergoes medullary excavation, and the change from concave, excavated, solid taps to convex layers of lattice-like horny columns gives to these places the structure of a cutaneous horn. They usually extend some distance over the surface, and represent those small sharp spots which one feels on stroking the skin.

But the greatest degree of hyperkeratosis is represented by large formations, from the size of a lentil to a shilling, in which the margin between horny and prickle layer is perfectly horizontal, the former

being heaped up to a height of three to five millimetres. Clinically, the horny layer, at such places, is not scaly, but has a thick, horn-like structure ; it is dark yellow and transparent, like cast horn. To this corresponds, histologically, the partial or complete disappearance of the granular layer, and the preservation of all the nuclei of the horny cells. A special hardness and density interferes with the separation of kerato-hyalin, as much as excessive moisture. All the sweat pores run through this nail-like substance, in a condition of dilatation, as do the openings of the larger sebaceous glands of the face, which, under such callosities, are usually distinctly hypertrophic.

This development of the process into callosities and corns would be very unimportant were it not that, here and there, underneath the horny layer, graver processes commence. On many sections, with slightly thickened horny layer, we see, among the regularly formed epithelial ridges, some which send very small but very irregular, a-typical processes into the connective tissue. This is, at such parts, always more cellular, its lymph spaces are dilated, and the elastic fibres atrophied to isolated fragments; the mast cells are increased in number, but there are as yet no plasma cells. These a-typical growths of the prickle layer, at the base of the callosity, assume, on other preparations, greater dimensions, and notably affect the otherwise simple form of the papillary body. The epithelial processes have a cylindrical, reticular or even acinous formation, are mostly small, show mitoses at the connective tissue margin, and are already surrounded by a dense cellular infiltration of the cutis. If this acanthosis takes place all over the callosity, it is elevated and fissured like a hard wart. As a fact, however, it is more ; it is a papillary cancer, which produces great epithelial growth. A specimen of this nature, the size of a cherry, showed, on the surface, the thickened, almost homogeneous, horny layer, sending broad horny taps into some of the thickest epithelial processes, while other epithelial taps showed inside them irregularly distributed hyalin pearls ; deeper down, they passed into coarse, reticular, epithelial processes, which were partially liquefied in the centre. This, as a whole fan-like, new formation has its smaller end in the under part of the cutis, and is margined by a small zone of plasma and mast cells, which sends processes outwards into the fine papillæ.

The carcinomatous change is much more rapid, where the acanthosis all along predominates. In place of the nail-like callosities, we note, on such places, scales, and later, hard crusts, which, when thrown off, leave flabby ulcers, which do not heal ; the cancerous ulcer.

The first histologically evident changes are very irregular expansions of the prickle layer, here a series of round buds, there broad plates and

small bent arms. But all these outgrowths remain in close relation to the thinned prickle layer. The whole process leads rather to a distortion than to a thickening of the prickle layer, and to this the increasing cornification contributes. But it is more important that the proliferation is limited to the basal prickle cells, and that the young cells of this layer, instead of adding to the upper layers, rather tend to separate themselves as an independent thin layer. At first this germinal layer forms folds under the rest of the prickle layer; there are formed wide (inter-epithelial) lymph spaces, and, ultimately, vesicular cavities* between the two, into which the upper remnants of the prickle layer project unchanged, while they are margined beneath by the thin, proliferating, irregularly extending germinal layer. The epithelial cells, constituting the latter, have lost their fibrillation and their prickles, and therefore resemble glandular epithelium, and this alone suffices to explain their separation from the prickle layer proper, as well as their tendency to combine into round balls and buds. The connective tissue shares in the process, with great dilatation of the vessels, gaping lymph spaces, considerable œdema, and a great abundance of spindle and mast cells—not plasma cells. Leucocytes and wandering mast cells are also found in the wide lymph spaces of the epithelium, along with œdematous, swollen, detached epithelial cells; and further, there are collections of fibrin and leucocytes in the thickened horny layer, which is thus transformed into a crust, which permits the growth of numerous saprophytic bacteria.

All this shows a certain resemblance of the elementary changes to those of the first stage of Paget's carcinoma of the nipple; but here the prickle layer is, as a whole, much more irregularly formed, and rather resembles, in miniature, ordinary cancer. The thin prickle layer, the lacuniform character of its protuberances, and the softening of the horny layer above, explain how ulceration gradually developes in the centre of such places. Before this occurs, progressive changes develope in the cutis, as in true cancer: there is a widespread dense layer of plasmoma tissue and a great number of mast cells. This granulation-like tissue forms the base of the ulcer, which developes after removal of the crust and discharge of the few remaining epithelial cells, while its lateral walls are still formed of proliferating epithelium, and thickened horny layer. From these lateral parts alone, the cancerous infection extends to the neighbourhood, and we understand why the ulcers so long extend only superficially. Here, as in Paget's carcinoma, the epithelial proliferation finds an important hindrance in the dense plasmomatic cellular infiltration, which strives to encapsule it, and we

* Here, as in Darier's disease, Auspitz's expression "acantholytic vesicle formation" is justified.

understand why these ulcers, though malignant, do not clinically give that impression. The dwarf-like carcinomatous growth of the border is almost completely concealed beneath the thick horny layer, and the surface of the ulcer has the appearances of healthy granulation.

But as time goes on all this is altered. From it, as from every "flat" cancer, there developes, in time, an ingrowing, spreading one. I have specimens of tumours at this stage, from the ear and from the eyelid. They were clinically distinguished from ordinary cancer of the face, by the absence of a firm marginal part; the ulcer of the eyelid had therefore almost the appearance of a Rodent ulcer. But I have never seen them cause swelling of the glands; and the ulcer of the ear is clearly distinguishable from Rodent ulcer, by the greater softness, the more active breaking down and the profuse secretion.

The histological appearances of the eyelid and ear are otherwise the same as those of fungating, coarse reticular carcinoma, which almost invariably developes from the surface, and now and again from the prickle layer of the follicle. To true Rodent ulcer of the eyelid, there is consequently no resemblance. There is here no reaction of the cutis, in the form of a fibrous, and further out a cellular new formation, all we have are small plasmoma areas in the interstices of the broad epithelial processes. But, on the eyelid, which had been previously operated on, these had not yet softened, and therefore the ulcer had still a dry appearance. On the ear, the epithelial processes are everywhere undergoing hyalin degeneration, are partly softened, and those lying next the ulcer, liquefied. From this coarse reticular kernel of the carcinoma, there extend, in different directions, cancerous processes, of cylindrical and reticular form, which run through the cutis without causing much reaction. This region is very rich in elastic fibres, and therefore, where the epithelial processes are compressed into broad masses, numerous elastic fibres are enclosed by them, and, owing to the small development of cellular infiltration, remain strikingly well preserved. With an elastin stain, the epithelial areas, speckled with stiff elastic fibres, present a characteristic appearance. As a matter of fact they are, as previously noted and as is seen by a good collagen stain, also penetrated by fine collagenous fibres, and in the neighbourhood of these fine, mesodermic passages, commences the softening and liquefaction of the epithelial blocks.

The reactive plasmoma of the cutis is therefore, in the whole process, only local and temporary; the new formation, at first lateral, and later growing downwards, meets no serious resistance, except where masses of cartilage or large hair follicles block the way. Here and in the widespread softening, which is no doubt connected with the great œdema of the stroma, I find the main difference between this carcino-

matous ulcer and the rodent. In that form first described, where a simultaneous superficial hyperkeratosis produces hard papillary cancers, the epithelial processes, at the base of the tumour, have a great tendency to liquefaction.

In these histological data lies the foundation of the clinical fact, that the cancer of sailor's skin is much more malignant than the true Jacob's Rodent ulcer, with which, at the commencement, it shows a certain resemblance, in its flat form and its localisation on the face, a fact, which I have unfortunately been able to verify on several cases, long under observation.

4. *Xeroderma pigmentosum.*

This condition, first described by Rüder, and by Kaposi, and since frequently observed in most countries, shows such a striking analogy to the "sailor's skin," just considered, that we may almost name the latter, "Xeroderma pigmentosum of adults." Like that, it developes under the influence of the rays of the sun, especially of the chemically active rays of the spectrum (blue to ultra-violet), and affects only the exposed or slightly covered parts of the skin. It begins, like the sailor's skin, with an inflammatory hyperæmia and a freckle-like collection—to protect the skin—of attracted brown pigment, and there is soon added a striking roughness of the surface, a formation of warts, and finally disseminated carcinosis—a stricter analogy there could not very well be. The main distinction lies in the fact, that the special weakness of the skin to the blue rays is, in the sailor's skin, acquired in adult years, while in Xeroderma pigmentosum it is congenital. Therefore the latter appears in early childhood, shows a hereditary distribution, and at puberty is more diffusely extended over the parts of the body exposed to light, and, with inappropriate treatment of the initial stages, has a still graver prognosis than the former. Possibly it is due to the earlier commencement and the longer duration, that, in Xeroderma pigmentosum, the deposit of pigment and the scar-like atrophy of the skin, with collateral venous ectasis (teleangiectasis), are more marked. But the latter are not altogether absent in the sailor's skin.

From my observations on two families, the following is the clinical course. In the second year of life, exactly corresponding to the time when the children get freely out, *the initial stage of erythrodermia*, shown by spotty (especially on the cheeks) or diffuse capillary *hyperæmia* of a livid red colour, a slight *puffiness* of the skin (especially on the face) and a striking *roughness* of the surface, appears; the skin

looks as if unwashed. This stage is that of inflammatory irritation by the chemical rays.

In the third and fourth years of life, pigmentation is always increasing—first in small, freckle-like spots (especially on the cheeks, forehead, and backs of hands) along with active scaling, and the transient appearance of flat warts, while the hyperæmia and œdema somewhat disappear. At this time commences the hyperæmia of the conjunctiva, and the photophobia. This is the stage of reaction of the skin to the influence of light; the loosened pigment acts as a protectant against the influence of light, but even already, it shows, histologically, its evil influence on the epithelium.

Not till the sixth or seventh year does the disease reach its full development. White or shining, mother-of-pearl spots appear between the pigmented spots, which have increased in number, size, and colour; they are without pigment or vessels, but are frequently permeated or margined by dilated *cutaneous veins*, so-called teleangiectases, which stand out from the white skin as red points, lines, and stars. But this *partial* sclerosis of the skin always affects only certain areas of predilection, such as the zygoma, the nose, the ears, thus the bound down, non-fatty parts of the skin, possibly because here the rays of light are not cut off by the presence of fat, and can penetrate to the innermost margin of the skin. The warty structures become more numerous, penetrate deeper into the cutis, and some of them, rapidly increasing, are converted into true *carcinomata*, others into *pigmented carcinomata.* More rarely there are developed, from the angiectases, a few angiomata; the occurrence of true sarcoma, though often described, is very doubtful; *Xeroderma pigmentosum is a typical carcinomatous disease.*

In this third stage, the acme of the disease, possibly owing to the continued increase of pigment, there is a constant tendency to growth (metaplasia) of the epithelium, which culminates in the formation of warts and cancers. This may, by appropriate treatment, be arrested or improved, otherwise it invariably leads to death from carcinosis. As in Rodent ulcer and sailor's skin, there is no swelling of the glands.

The first stage of erythrodermia does not appear to have been available to any of the numerous investigators. Pollitzer believes that the initial hyperæmia is accompanied by exudation of sanguinolent serum, and that the breaking down of red blood corpuscles produces the pigment in the prickle layer. Neisser, on the contrary, maintains that all the pigment is of a melanotic nature, and is not due to hæmorrhage. I also have only a series of pieces of skin from two brothers of the family, first described by Rüder, which are all taken

from the acme stage. So far as these permit of any conclusions as to the initial stage, the assumption of Pollitzer appears to me at least unnecessary, for we have certainly to do, from the commencement, with a true melanosis of the skin, and an initial production of pigment from the blood would not explain the pigmentation in the second and third stage, where the inflammatory hyperæmia has disappeared. Since, at the acme, the changes of the skin are strictly limited to the region from the sub-papillary vascular net outwards, the erythrodermia, hyperæmia and inflammatory exudation of the first stage probably have their margin under the uppermost layers of the cutis. Since, further, the horny layer is distinguished, all along, by an abnormal dryness, the epidermic changes can hardly be secondary to exudation in the papillary body, but are induced by the direct chemical action of the sun's rays. I do not care to draw any further conclusions, as to the earlier stage, from the later appearances.

The second stage, characterised by small, brown, freckled pigmentation, with persistent roughness of the surface, is fully explained by my preparations, for such parts persist everywhere between those more developed. At these places, the under angles of the epithelial ridges, and also other small areas of the basal prickle layers, are densely permeated by black-brown pigment, and altered in a way to be immediately described. The papillary body, under these collections of pigment, is widened, mainly from dilatation of the venous capillaries and a multiplication and swelling of their perithelia; the endothelial cells of the blood capillaries are also largely swollen and abnormally rich in protoplasm. These changes of the connective tissue are, however, by no means limited to the pigmented regions of the epidermis, being found in different degrees between and around them, diffusely extended over the whole xerodermatous skin. We cannot, therefore, ascribe the abnormal pigmentation of the epidermis to the chronic inflammation of the papillary body. Nor can the dilatation of the superficial cutaneous veins be made answerable for it. This is certainly excessive at certain spots, so that we see the commencement of small cutaneous varices, macroscopically evident as blood-red points. But these places are by no means those of epidermic pigmentation, indeed, on my preparations, the one appears to exclude the other. Finally, it must be noted, that neither in the neighbourhood of the dilated veins, nor in the inflamed hypertrophic papillary body are there visible any escapes of red blood corpuscles, or pigmentary remains of them. Thus, on these areas of the slightest development of the disease, there is no evidence of a development of the pigment from diapedesis of blood corpuscles, or even from diffuse colouring matter. The pigment rather shows the qualities of pure

melanin, and appears, like the inflammatory parenchymatous exudation of the papillary body, though independent of it, to be attracted, by the chemotactic influence of light, towards the surface. For this view we have the following arguments :—

The pigment is, on the least pigmented spots, not limited to the basal prickle layer. Streaks and clumps of it are found in the adjacent papillary body, partly free in the lymph spaces, partly on and in the hypertrophic spindle cells, but not in the direct neighbourhood of the blood vessels. They show, in their distribution, as a whole, a tendency towards the pigment of the prickle layer, in that certain paths are recognisable, which combine the cutaneous pigment with the epithelial. And further, we find, on the least affected, pigmented spots, scattered streaks and clumps of pigment in the upper prickle layers, and even in the form of smaller streaks in the granular and horny layer. These connected collections of pigment, reaching from the papillary body to the horny layer, convey the impression, that they have been somehow attracted from the blood stream to the surface of the skin ; none of the new pigment theories, except the chemotactic, appears to me to harmonise with this form of distribution. Were the pigment developed at the main seat of collection in the basal prickle layer, and carried from there into the cutis by the lymph stream, there would be no reason why the same lymph stream should carry the pigment in an opposite direction, and the relatively rich and quite unusual collection of pigment in the horny layer would remain unexplained. On the other hand, were the pigment connected with definite pigment-carrying cells of the epithelial cutis margin, the last named observation would still be inexplicable, but, as will be immediately explained, there are no special pigment-carrying cells.

The prickle layer, as a whole, is not exactly widened, but, on the pieces of skin of the face before me, the epithelial ridges are more numerous and broader than usual. The granular layer is two or three rows thicker, and the horny layer much thickened. It is split into lamellæ, which, towards the surface, are irregularly folded, and here and there beset with small streaks of pigment. The important symptom of roughness of the surface is therefore not the result of greater exfoliation, but of a distinct hyperkeratosis. Probably there is a slight hypertrophy of the prickle layer ; there is certainly a great delay of cornification (widening of the granular layer), and a compression of the horny layers into a hard horny covering, folded on the surface.

Finally, I must once more refer to the nature of the pigment, and its influence on the epidermis. The pigment consists of brown granules

of different size, which partly form free masses, of the shape of the lymph spaces, and, partly entering into the protoplasm of the connective tissue and epithelial cells, colour these more or less brown. In the connective tissue cells, this pigmentation takes place without any other distinct changes of the protoplasm; but it is otherwise in the epithelial cells. Here also the pigment partly extends outwards, in fine inter-epithelial streams. It is partly taken up by the protoplasm of the epithelial cells, and in two fundamentally different ways. The one form of pigmentation is the normal one. The pigment finds its way into the interior of the epithelial cells, without staining the outer body of the cell, I believe by means of the fine lymph spaces, which I have described as accompanying the nerve terminal in its entrance into the cell. It then collects, as usual, between nucleus and protoplasm, mainly at the distal nuclear pole, and stains, from here outwards, the distal endoplasm of the cell. But, in addition to this normal pigmentation of the cells, there is present, from the commencement, an abnormal variety of pigmentation, directly from the inter-epithelial lymph spaces into the ectoplasm of the cells. For this, the outside of the cell, clothed with prickles, is evidently little adapted, but we see that these disappear under the influence of the adjacent pigment, and in the same degree as this occurs, the cell body is stained darker and darker. At first we see, if the prickles are well stained, the pigment granules lying in rows between them; then the prickles and the whole epithelial fibrillation disappear, but only so far as the pigment penetrates the cell. We may often enough find basal prickle cells, which, at the side where they are pigmented, have no prickles, and are some distance from the neighbouring cells. It may be that the hardening in alcohol causes the softened cell body to shrink, at such places, more than the rest of the protoplasm, but this assumption alone is not sufficient to explain the remarkable width of the adjacent lymph spaces. The main factor is the loss of the connecting bridges and the epithelial fibrillation; it is due to this that the cells are so widely separated from their neighbours, and converted into amœboid, pigmented lumps.

This second pathological variety of pigmentation is consequently accompanied by an extensive transformation of the epithelial cells, a metaplasia; the prickle cell becomes a formless, amœboid cell. The pigment appears to possess directly solvent properties on the prickles and the fibres. This change of the prickle layer, under the influence of the pigment, may be recognised, even with a low power, from the considerable spaces, which appear mainly in the basal prickle layer, and surround the pigmented cellular clumps. Where many of these pigmented cells lie together, the regular arrangement of the prickle

layer is in parts completely lost. The nucleus resists the influence of the pigmentation much more than the cell substance; even in the formless pigmented clumps, lying close in the dilated lymph spaces, one can recognise, from the regular oval form and the size of the nucleus, their epithelial origin. This resistance of the nucleus is all the more important, as it explains the meaning of certain branched structures, which recall the "chromatophores" described by different authors. These are small, elongated epithelial cells, which usually commence in the basal prickle layer, but whose upper end extends, with fine protoplasmic processes, into the lymph spaces at the distal end. The cell body, as well as the processes, are deeply pigmented, and in the former the characteristic epithelial nucleus is still clearly recognisable. Evidently the amœboid transformation of the prickle cell has gone so far, that the whole, now movable, pigmented epithelial cells follow the general pigment stream outwards, and by the penetration of their protoplasmic processes into the lymph spaces of the surrounding epithelium, assume polypoid and spider-like forms. Probably it is these which, though they are only rare in Xeroderma pigmentosum, are regarded as chromatophores. Usually in this disease, the pigmented cells form, not branched, but rounded, lumpy figures and collections of such.

The third stage shows, along with an increase of the symptoms described, certain new ones. The thickening of the horny layer increases at some places to callous deposits; the granular layer there is much widened, but now and again disappears under the pressure of the horny callosity. The prickle layer is very much deformed, corresponding to the deep brown or black pigmented spots. Two particularly characteristic types are constantly recurring. The basal prickle cells may retain their cylindrical form, while they take up pigment and lose their prickles; they are then distinctly elongated, and since they no longer possess the necessary resistance, are frequently bent or twisted, and between them appear equally elongated, very wide, pigment-containing lymph spaces. There are found complete papillary apices, surrounded by thus altered prickle layer, which rests on the cutis margin as with a whole series of single feet. In this form the connection of the basal, cylindrical cells with the upper prickle cells is still preserved. But if the whole fibrillation of the basal prickle cells atrophies, they round off, and, running together, form large, rounded clumps, the lymph spaces around them dilating to a corresponding degree. This second form is more often found at the base of the epithelial ridges, where no papillæ are present. With a low power it appears as if completely black, large, solid lumps of pigment were scattered loosely in the under zone of the prickle layer, and the

epithelial cells there were absent. But with a higher power we see that the pigmentary lumps consist of closely-packed epithelial cells, in which the nuclei may still be distinctly recognised.

But it cannot be denied, that in certain parts of the preparations, similar metaplasiæ exist, with deformities of the epithelium, where only single pigmentary granules exist between and in the epithelial cells. I can only explain these appearances by the assumption, that here an ordinary pigmentary degeneration has taken place, and that the pigment has subsequently, possibly by the metabolism of the epithelial cells or by centrifugal force, been largely removed. But this occurrence is exceptional; we usually find a definite proportion between the amount of pigment and the extension and severity of the pigmentary degeneration of the epithelium. There exist, at the seat of greatest pigmentary invasion, quite astounding distortions and transformations of the prickle layer, so that often only two or three rows of prickle cells remain beneath the granular layer. The branched, pigmentary epithelial cells are here completely absent. The regular collection of pigment at the distal nuclear pole is then frequently found in the uppermost prickle layers.

To the maximal pigmentary changes in the epithelium, correspond those in the papillary body and in the upper half of the cutis. The papillary body is thickened, and shows an active multiplication of the connective tissue cells, which are usually smaller, spherical, and show little protoplasm. Such an infiltration with connective tissue cells frequently occupies the upper part of the cutis proper. The papillary body and the cutis are in general permeated to the same extent by pigment, but cellular infiltration and deposit of pigment bear no relation to one another. On the contrary, we frequently find the pigmentation greatest and deepest in the connective tissue, where it is also most distinct in the epithelium. In such places the collagenous tissue is permeated by a coarse, almost black net of pigment, passing directly into the open pigmented lymph spaces of the prickle layer. With a higher power this pigmentary net may be analysed, partly into free granules and coarse fragments, of dark brown colour, which almost fill the lymph spaces, and partly into melanotic, blackish-brown, spindle-shaped and spherical connective tissue cells, lining the pigmentary channels.

Here we have simply to do with a pigmentary infiltration, analogous to the pigmentation of the lymphatics in the epithelium; pigmentary degeneration of the cutis and the papillary body hardly occurs; the connective tissue elements withstand the pigmentary invasion much better than the epithelium. And yet there *appears* to be, here and there, a remarkable exception; but as I say at once, it is only apparent.

Several of the small, warty spots before me show a striking collection of cells and pigment in the papillary body and in the upper half of the cutis, so that these parts are three or four times thicker than the neighbourhood, and the epidermis is arched over them. It appears like a dense felt-work of spindle-celled or fibrous, nucleated tissue, whose cells and fibres are covered with pigment, as if with dust. On more close examination, and especially with the assistance of some good stain for collagenous substance, we find that these tumour-like formations only contain very few thin rafters of collagen, and consist mainly of closely-packed cells, without any trace of inter-substance, which contain vesicular, usually oval nuclei, and whose external mantles are covered with rows of pigmented granules. These form, when they are more spindle-shaped, large, fissured, where they approach more the spherical form, large, rounded alveoli, which they completely fill, and from which, on fine sections, they often drop out. In many places there are found, inside these pigmented cellular masses, irregular, winding cavities, with pointed processes, which exactly resemble the dilated lymph spaces of the prickle layer above, when affected by pigmentary degeneration. Were all these criteria not sufficient to distinguish this cellular tumour as epithelial, one is able to convince himself, though certainly only here and there, of its nature, by finding particularly deep, penetrating epithelial ridges, passing directly into the cell masses.

Certainly, to anyone who has not studied the soft nævi, and especially the pigmented nævi of early childhood, it must appear very remarkable, that these areas of prickleless cells, mostly lying enclosed in connective tissue, looking like a miniature spindle-celled sarcoma, are regarded as epithelial. The appearances are the same, here as there, and I must refer the reader for greater details to the chapter on Nævi. Here it may just be mentioned that, according to my experience, these cells are epithelia, which in the early or embryonic period of life, losing their prickles, grow into the connective tissue, and there lie ensnared. We are dealing, in these warty spots, with something special, with a nævus, and this is, like the rest of the skin, affected by Xeroderma pigmentosum—the nævous cells undergo pigmentation like the epidermic epithelium, and partly also pigmentary degeneration, accompanied by the formation of lacunæ.

This is, as we shall show, of considerable importance in determining the nature of these tumours, which develope in Xeroderma pigmentosum. In general, it gives us only another confirmation of the fact, that the invasion of pigment acts detrimentally only on epithelial, not on true connective tissue elements.

In addition to the dark pigmentary spots and the hyperkeratosis, the acme of Xeroderma pigmentosum is characterised by linear and

stellate venous ectases, and some strikingly white, sclerotic spots; the brown, black, red and white spots together make up the well-known, piebald picture of the disease. In the estimation of these symptoms, I agree with the most recent worker, Pollitzer, who attributes the teleangiectases to collateral stagnation, and the obliteration of the capillaries to hypertrophy and sclerosis of the connective tissue. It is evident, even clinically, from the chalky to mother-of-pearl colour of these spots, that a whole capillary region is obliterated, but whether this is the manifestation of a local atrophy of the skin, or the result of a sclerodermatous change, remains for histological investigation to decide. And the distinction is not without importance. For the spots are not only generally regarded as atrophic, although thorough investigation of the differences of level shows me no depression, as in true atrophy, but some authors lay so much weight on this atrophy, that they speak of a termination of Xeroderma pigmentosum in atrophy (Neisser), or suggest that it be named Atrophoderma (Crocker).

In order to decide this question, I excised a perfectly white spot, which lay between two venous ectases, from the nose of one of my patients. With it we were not exposed to the error, easily possible on the eyelid, of mistaking the normal thinness of the skin for atrophy. We found, as was to be expected, an almost complete absence of the papillæ and the papillary body, and a proportional diminution of the superficial capillaries. The prickle, granular and horny layers are broad, the epithelium is thus, as a whole, by no means atrophic. The under margin, towards the cutis, forms an irregular line, and the basal prickle cells vary much in size. But there is no projecting system of ridges, and consequently no papillæ. The epidermis rests, as a uniform plate, on an elastin-free cutis, consisting of thick, hypertrophic, collagenous fibres, and still containing an excessive number of spindle cells. A single blood capillary, reaching to the surface, is completely filled with closely packed, leucocytic nuclei; such white thrombi, in place of the original papillary vessels, indicate an unusual resistance to the papillary circulation. Pigment is present, neither in the cutis nor in the epidermis.

This condition, which, to judge from clinical appearances, would correspond to all the white spots, cannot possibly be regarded as an atrophy. The epidermis and the collagenous tissue are, rather, hypertrophic, and only the circulatory system undergoes atrophy. The skin most nearly resembles certain circumscribed sclerodermata, and a partial termination of the affection in sclerosis would be a better description than one in atrophy. We cannot therefore reckon Xeroderma pigmentosum, on account of its distinct commencement with inflammatory hyperæmia, and a supposititious development into atrophy, with

the Ulerythemata, from which it is also separated by its invariable termination in carcinosis, and its etiology.

If we are to regard the white spots as the results of a collagenous hypertrophy, before which the delicate tissue of the papillary body disappears, it is natural to attribute the disappearance of the papillary circulation to the same. At all events the reason does not lie in a primary change of the deep cutaneous vessels, for, like several investigators (especially Vidal), I found them normal. The whole affection runs its course on the surface of the skin, in relation to the epidermis, the papillary body and the upper half of the cutis, and leaves the lower cutis and the hypoderm intact. The disappearance of the capillaries is consequently either the result of the hypertrophy of the surrounding tissue, or, along with that, the common result of a common cause. That, on its side, is either the cause or at least the adjuvant of the appearance of the venous ectases.

The latter I have found on the most varied parts of my preparations, and they evidently correspond to the red points and lines, noted clinically. Since we never find blue points and lines mixed with the red, we must assume that all the venous ectases in this affection have a superficial situation, and this also indicates a resistance to circulation, limited to the surface of the skin. I am therefore in accord with the view of most authors, that the development of the teleangiectases is connected with the white spots; from the diffuse capillary hyperæmia, there developes, by disappearance of many capillary areas, a limited collateral hyperæmia, with resultant ectasis of the venous capillaries. I have not been able to recognise any new formation of vessels, in connection with the red lines and points.

If, before we turn to the destructive termination of the affection, we consider once more the apparently so irregular, varied appearances which it produces, from the uniform etiological aspect, a common principle can hardly be denied.

The pigmentation and the hyperæmia of the surface, in the form of capillary hyperæmia and venous ectasis, the hyperkeratosis and the sclerosing of the surface of the skin, are simply different endeavours of the skin to paralyse the injurious influence of light. The pigmentation does this most simply, and as a whole most innocently, the brown colour of the pigment directly absorbing the light and transforming it into heat. And since the pigment has the power of penetrating to the horny layer, it fulfils its duties most certainly and thoroughly. But, as we have seen, the epithelium suffers by increased accumulation of pigment, and may be converted into movable and dangerous pigmented epithelium; and the same danger exists for all soft nævi of the skin.

The collection of blood on the surface arrests, like the red glass of

photographers, all the blue rays, and may therefore also be regarded as a protectant. But in so far as the epidermis is still exposed to light, the hyperæmia is not fully protective, while it leads, in addition, to other permanent nutritive changes. The hypertrophic changes in the connective tissue and epithelium are, so far as they are not the direct results of the action of light, no doubt to be attributed to this hyperæmia, which only diminishes when the pigment appears. Most innocent is the venous ectasis, and a fiery red nævus would do everything, which the inflammatory redness and the teleangiectases together seek to do.

In the opposite way to the collections of blood and pigment, the other changes, the hyperkeratosis of the epithelium, and the sclerosis and capillary atrophy of the papillary body, evidently reach the same goal. They make the cutaneous tissue less sensitive, drier, harder, and more tendonous and callous. They do not arrest the light, but they diminish its influence.

All these, one after another, occur, and since they are not all equal, we have this varied mixture of them, which, at the first glance, suggests anything but a uniform process.

It is hardly necessary to discuss more closely the other, and especially the deeper constituents of the skin. Many of the changes, which are occasionally noted, are certainly without general significance. The follicles, hairs and sebaceous glands do not, in general, suffer, and are found atrophic, only in the sclerotic parts. An obliterative arteritis is indeed often found in the deep blood vessels, but it is not necessary for the explanation of the superficial sclerosis of the cutis. It is worth noting, that, in all my preparations, the coil glands are strikingly large, have broad loops and widely dilated lumina. On such a soil developes the carcinosis of Xeroderma pigmentosum.

The four malignant tumours, which I have, are all true carcinomata, and unpigmented. They all developed from the surface epithelium and are of the fungating form. They all developed pretty rapidly, resembled actively proliferating ordinary warts, had a firm consistence, and, as they increased, showed a somewhat folded, but not moist or hæmorrhagic surface. The histology corresponded to the clinical appearance; a broad layer of epithelium mainly over the surface of the skin, to a less extent in it; the almost papillary form of the surface passed, lower down, into the coarse reticular, and at the base usually into the simple reticular form. The amount of vascular connective tissue is very small; the persisting papillæ are delicate and do not reach to the surface, the new growth is therefore particularly hard and dry, and there is no loosening and breaking up, as in the pure papillary cancers. But, like this latter, the epithelial growth finds an important hindrance to its invasion in the cutis of the neighbourhood and in the hypoderm. In

Xeroderma pigmentosum this hindrance is due to the atrophic and sclerotic conditions of the cutis, which usually form the base of the epithelial growth. The carcinomata are therefore the more benign, and remain the longer in the stage of a superficial wart, the greater are the regressive changes of the cutis. The resistance of the cutis is evident, everywhere in my preparations, in the fine, pointed, thin epithelial buds, which form the basis of the tumour, and often run together into a very fine, reticular layer, without being able to penetrate into the neighbouring cutis. The cellular infiltration of the cutis around is usually not particularly marked. But this depends very much on the accidental seat of the tumour. In a coarse reticular carcinoma, the size of a cherry, which developed on the pretty normal skin of the angle of the mouth, the cutis beneath is permeated by a dense plasmoma. Here, at one side of the base, the carcinoma has penetrated into the neighbouring cutis, and has reached about one millimetre, in pure cylindrical form, inside the apparently normal neighbourhood—an ominous extension, which was fortunately completely extirpated.

We see then, that, on such patients, a very large number of successful operations may be done, but that, on the other hand, the ultimate exclusion of general carcinosis depends entirely on the absolutely complete extirpation of the carcinomatous nodules and the prophylactic improvement of the whole epidermis, in order to avoid the recurrence of carcinomatous warts. The numerous carcinomata of the children in the family first described by Rüder, have, so far as I can observe, all more or less the warty or button-like character, and therefore closely resemble the carcinomata of sailor's skin, while they are clearly distinguished from the much flatter initial stages of Jacob's cancer. In their later extension they lose all their characteristics.

Most authors have, in examining the malignant tumours of Xeroderma pigmentosum, also found carcinomata, and the few exceptions seem rather to confirm the rule, when they are more thoroughly examined. Chiari found, in one case of Pick's, a spindle-celled, pigmented sarcoma, and stated that the case corresponded, histologically, with the appearances of a sarcoma, developed from a pigmentary nævus. As I shall show in the chapter on nævo-carcinomata, these cases of apparent sarcoma are always true carcinomata, of peculiar type. Elsenberg found a "giant-celled sarcoma." The giant cells had no resemblance with Langhans' giant cells, and enclosed a carcinoma nodule (!). The whole tumour showed very little (!) inter-cellular substance, and so on. Pollitzer recently found, in a tumour from Crocker's case, an inextricable mixture of spindle-celled and round-celled sarcoma, myxoma, and carcinoma.

If we consider what I have said above of the small pigmentary,

warty elevations present in Xeroderma pigmentosum, which are no other than ordinary soft nævi, pigmented by the disease, which, with a low power, are confusingly like small sarcomata, we are very much tempted to assume that, where in actively growing tumours in the course of this disease the histological appearances of pigmentary sarcoma develope, we are only dealing with those carcinomata which, instead of from the surface, develope from pigmented nævus cells, *i.e.*, with the so confusing nævo-carcinomata. Such a suspicion is still more justified by those mixed tumours, which Elsenberg and Pollitzer have described; it is too little known that nævo-carcinomata especially tend to produce astonishingly large spindle cells and giant cells of epithelial origin.

If, as is probable, we are dealing in all cases with ordinary or with nævo-carcinoma, the appearance of a myxomatous tissue, such as Pollitzer describes, is comprehensible. But in my carcinomata I have not observed it.

Whether the occurrence of angiomata is proper to Xeroderma pigmentosum, as Taylor believes, further experience must show. True angiomata sometimes develope elsewhere on the basis of long persisting angiectases, and might readily develope in this affection; but their presence must be very rare, compared to the capillary venous ectasis. In a case of Xeroderma pigmentosum, which I had ten years under observation, there was found, in addition to numerous angiectases, especially of the face, only one single cutaneous, dark-red nodule, the size of a pepper-corn, on the back of the hand. While all the angiectases underwent changes, appeared and disappeared, this remained always the same, and when I recently removed it, it proved to be, not a true angioma, consisting of arterial capillaries, but a small, pretty well defined venous nævus (see angiomatous nævi).

From this discussion we see that Xeroderma pigmentosum does not give origin—as the different statements appear to show—to all possible tumour formations, but, like the sailor's skin, is especially disposed to carcinoma, and on this ground, as a carcinosis with a very well-known history, I have classed it here.

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5. *Paget's Carcinoma of the Nipple.*

This disease, first described by Paget as a particularly ominous form of eczema of the nipple, has the special significance in the doctrine of cancer, that the flat disease of the surface epithelium, which gradually passes into true cancer, does not possess, like Xeroderma pigmentosum and sailor's skin, a dry, firm, horny, and particularly rough surface, but a moist, soft, weeping one, which leads to its being at first regarded as a catarrh of the skin. There is here the same distinction between the different preliminary dermatoses of carcinoma as between the hard and soft carcinomata of the skin itself; the fungating and cylindrical on the one hand, and the alveolar and infarctive on the other. And, as a fact, we find that the cancers, which are secondary to Xeroderma and sailor's skin, take the cylindrical, those following Paget's disease of the nipple, the alveolar form.

The disease commences stealthily, in women usually over forty, and for a long time seems merely a resistant recurrent crust or fissure of the nipple, which latter shows a tendency to retraction. Gradually the nipple and the areola are transformed into a sharply circumscribed, dark red, moist, crusted surface, which extends concentrically, more rarely by satellites, never heals spontaneously, and does not respond to anti-eczematous treatment. On the diseased surface there is constant alternation of flat exfoliations, deep erosions, true ulcerations (especially in the centre of the nipple) and temporary cornification, and consequently alternate itching and pain. In almost all cases, usually after seven to ten years, there appears in the centre a superficial, ulcerating, or a deep, nodular cancer. Swelling of the lymph glands only accompanies the last stage of the general cancerous cachexia.

Considering the rarity of the affection, it has been very frequently examined histologically. The first examination was that of Paget's cases, by Butlin. He found the prickle layer very much thickened and actively proliferating, the cutis inflamed and densely infiltrated with cells, the ducts of the mammary glands dilated and filled by cellular proliferation, the glandular epithelium proliferating, and ducts and glands surrounded by leucocytes. He believed that the newly-formed cells, which fill the glands, and later burst their walls as cancer cells, developed from endogenous division. He regarded the changes in the surface epithelium and in the glands as similar processes.

The next, more important work is that of Thin. He noted that the epidermic changes began suddenly at the border, and, extending from the border to the centre, led to the breaking down of the epithelium; the sub-epithelial inflammatory zone was thickened in a corresponding degree. From the breaking down of the prickle layer, there remained a sort of framework, consisting of the œdematous and vacuolated cell bodies of the persisting epithelial cells, from which the nuclei had often fallen. The vacuolated cells are found at the most recent, marginal points of the affection. Thin draws attention to the limitation of the cellular infiltration to the papillary body, and to the

freedom of the cutis proper. He does not find, like Butlin, in this characteristic epidermic affection, any traces of eczema.

Duhring and Wile found in the prickle layer the symptoms both of new formation and degeneration. The prickle cells are mostly voluminous, and contain one or two nuclei. In the inter-papillary prickle layer, the cells are concentrically arranged in two zones, a central degenerating and a peripheral proliferating one. From the surface epithelium, the degenerative and proliferative processes extend into the lactiferous ducts, which are filled with cast epithelium, then to the glandular epithelium, which finally, as cancer, breaks through into the stroma of the gland; the scirrhous character of the cancer causes the retraction of the nipple.

Five years later, Darier discovered a new aspect, maintaining that in four cases of Paget's disease he was able to determine a psorospermosis. He found the same coccidia as in his universal "psorospermosis" of the skin, and he therefore ascribed the appearances of degeneration of the epithelium to the immigration of animal parasites. The coccidia of this affection are, in general, somewhat larger than those found in his psorospermosis, and show, in abundance, forms, which only appear there after long culture outside the body. Darier found the coccidia in Paget's disease, not only in numbers in the surface epithelium, but even in the lactiferous ducts, and in some cases even in the cutis, as well as in the proliferating epithelium of the nipple.

Owing to this discovery, Darier requested another Parisian investigator, Wickham, to thoroughly investigate, anew, the pathogenesis of Paget's disease. He first published his results, which completely confirm those of Darier, at the international Paris Congress (1889), then more fully in the Archiv für experimentelle Medicin, and finally published a comprehensive monograph, which very much facilitates the study of the literature on the subject. Wickham's work has a special interest, in the publication of the further personal experience of Darier, and from it I take the following description of the coccidia.

Among the cells of the prickle layer there are many, which, by their unusual size, their deep stain, the absence of prickles and other granulation of the protoplasm, the size of the nucleus, but especially the retraction of the protoplasm, stand out from the surroundings, and, therefore, indicate their difference from the prickle cells. By the retraction of the protoplasm, there develope apparently empty spaces at the periphery of the cells, which are mainly to be ascribed to coagulation by the alcohol. Some of these bodies have a hyalin membrane, which remains adherent to the surroundings, when the protoplasm retracts, so that the vacuoles develope between it and the remains of

the protoplasm. In alcohol preparations it is not easy to demonstrate the inter-epithelial seat of these bodies, but it may be done in some cases. They are seated mostly in the lowest and second lowest row of prickle cells, but are here seldom encysted, while, higher up in the prickle layer, they usually have a thick membrane, and are often of considerable size. The moderate distribution of these bodies in the prickle layer indicates the first stage of the cutaneous affection; they are found at its border. Where the erosion extends deeper, the prickle layer is converted into a net, by the numerous vacuoles, and the retracted parasites are here not easy to distinguish from deformed epithelial cells. The rest of the degenerated prickle layer is beset with parasites and leucocytes, and dries up into a crust—Darier's second stage. In his fourth case, this investigator found very voluminous cysts, at the border of an ulceration, filled with oval bodies of an indefinite nature.

In this case, which had lasted for eleven years without the development of cancer, the upper cutis layer, immediately underneath the small papillary zone of infiltration, is sclerotic, formed of stiff, non-wavy connective tissue bundles, parallel to the surface, showing only slight indications of fibrillary structure, and containing no elastic fibres. Underneath this sclerotic layer the skin is normal, as are the coil glands and ducts, while the sweat pores swarm with parasites. The hair follicle epithelium is beset with coccidia, and very much degenerated, the hairs have fallen out; the lobules of the sebaceous glands also contain coccidia, and, with the hair follicles, are surrounded by a very active zone of inflammation. The very frequent incongruity between active changes of the cutis and few coccidia in the epidermis, Darier ascribes to the recent affection of fresh, newly-developed epidermis, by the parasites.

Wickham everywhere agrees with Darier, and there is therefore not much more to be noted. According to him, the leucocytes in the first period are easily distinguished from the initial stages of the parasite, by the following characters. They are elongated, always lie between, never *in* the epithelial cells; their nuclei stain deeply with carmin, and also appear elongated, but their protoplasm is indistinctly margined. The youngest forms of the parasite, on the contrary, are particularly irregular in form and size; they themselves stain deeply with carmin, show no nucleus, and are frequently seated in the epithelial cells. He found them very frequently in the fine scales of the surface, and also determined, outside the cancerous growth, horny pearls in the affected surface. The retraction of the nipple, he ascribes to the very great connective tissue sclerosis around the lactiferous ducts. The origin of the cancer is by no means always limited to the

latter and the parenchyma of the gland ; in two of his cases, Wickham found it in the surface epithelium.

I have, thus fully, repeated the observations of Darier and Wickham, so that the reader may form his own conclusion as to what these authors have observed. Since I have myself observed and examined a typical case of Paget's disease, I was in a position, critically to investigate the individual points, on which they lay value in the theory of psorospermosis. But since there are sufficient positive facts, quite independent of the doctrine of psorospermosis, which the study of these preparations discloses, I believe it will be better to state them first, without reference to Darier's theory.

My view of the affection corresponds in the main with the older

FIG. 27.—Paget's Disease of the Nipple.

P. Plasmomatic Infiltration. *V.* "Vesicle" formation. *M.* Mitosis.
O. Œdematous prickle cells.

ones of Thin, Duhring, and Wile, and also with the most recent one of Karg. Like these investigators, I recognise the most important change in a peculiar degeneration of the prickle cells, which we may regard as a peculiar form of epithelial œdema. With a low power, we see that, exactly at the border of the affection, the ridges are very much thickened, enlarged, and all of them rounded. The papillæ between the ridges are naturally also rounded ; they are œdematous, swollen, and cellularly infiltrated. Even with this power we note, scattered in

the ridges, clear, round and oval spots, which are seen with a higher power to be gigantic epithelial cells (15-30μ), which contain either a very large nucleus with much chromatin, or, instead of that, a mitosis. We see next, that the amount of mitosis in the prickle layer is extraordinarily great, even exceeding that in acuminate condylomata, and carcinomata. In many of the ridges, a fourth of the cells are mitotic. The non-mitotic œdematous cells have in common with the mitotic ones, that the nuclear substance is deeply stained, and occupies the centre of the cell, and that the surrounding, very broad, protoplasmic halo only shows a small quantity of reticulated, very faintly-stained substance, along with much unstained. There are also many non-œdematous mitotic cells, but it cannot be denied, that this form of cellular œdema closely resembles the physiological œdema of mitosis, and especially affects those cells undergoing mitosis. All these œdematous and mitotic epithelial cells compress, by their increase, the adjacent epithelial cells, which are arranged around them, into deeply staining cellular rafters. Their varying position inside the prickle layer, and especially inside the ridges, therefore induces altered relations of the whole prickle layer. Occasionally, the œdematous cells are regularly scattered, and the prickle layer is only distended as a whole. As Karg notes, the cells, at the undermost angle and the outer border of the ridges, are often heaped up, and then appear quite pale. I found, still more frequently, that zonal arrangement described by Duhring and Wile. With a low power it appears as if two ridge systems were stuck into one another. Directly on the papillary body is seated a series of little altered, simply flattened and mitotic epithelial cells; then follows a second, and finally a third row, which contains so many œdematous cells that it looks almost like an unbroken row of spaces, which separates the outermost epithelia from the solid heart of the ridge. If the epithelial ridges are small, the inner kernel of solid epithelium is absent, and on an external solid mantle, there follows only the reticulated centre. Finally, there are areas of the prickle layer, in which the cellular œdema is so great, that only a coarse vacuolated net of epithelial rafters remains.

This system of spaces is distinguished from the ordinary inter-cellular vesicle formation by the fact, that there are here no dilated lymph spaces but only excessively liquefied, cellular substance. Therefore the better the hardening of the parts, the more are the spaces merely apparent, and permit the recognition of the completely cleared cell body. The lymph spaces, on the contrary, around the swollen cells, are everywhere diminished and obliterated. The cellular œdema rather resembles the reticular degeneration of the epithelium, since here also the vacuoles appear in the outer part of the cell body. But from that

it is distinguished by a remarkable circumstance, namely, the complete disappearance of the epithelial fibrillation and the prickles, which latter persist in reticular degeneration.

If we stain the epithelial fibres and prickles with Kromayer's or some other iodine method, we get appearances, which throw some light on the nature of this œdema. Whenever a cell swells up, its fibrillary system disappears. Thus it is that the cells assume such enormous dimensions, become so completely rounded, and separate so readily from the neighbouring cells, and therefore they so much resemble mitotic cells, in which the fibrillary system is temporarily lost. Now we understand also the formation of sharply separated areas inside the prickle layer; the unfibrillated, swelling epithelial cells form clumps or alveoli inside those prickle cells still adhering by their fibres, and these arrange themselves as solid compressed rafters or nets, around the softened, swollen cells and cellular areas. If the alcoholic action is greater, the softened cells often retract, in the form of festooned processes, from the neighbouring cells, and then lie, with sharp refractile borders, almost isolated in the centre of the cavity. This border corresponds to the compressed fibrillary system of the neighbouring cells, and of course does not extend to the softened cells, whose fibrillation is already lost.

In the upper layers of the prickle layer, close under the horny layer, where the ecto-fibrillation of the epithelium is very hard and resistant, there is, now and again, another form of œdema of the protoplasm, in which the resistant ecto-fibrillation is compressed by the swollen inner zone of protoplasm, to which it forms a shell. We see then a homogeneous ring, larger than the neighbouring epithelium, but, in comparison with the completely afibrillary cells of the lower prickle layer, comparatively small. It contains, in the centre, the somewhat enlarged nucleus, and between nucleus and mantle, the frequently festooned, retracted protoplasm. At the same places there are also larger, shell-like, "encysted" cells, which have applied to their membraneous coverings complete, nucleated and therefore signet-ring-like, compressed neighbouring cells. But these encysted forms of œdematous cells are by no means frequent in my preparations. They represent a persistent zone of cornification, with advanced œdematous changes of the epithelium, two conditions, which are not often combined.

The cellular œdema and the disappearance of the epithelial fibrillation usually lead to diminished cornification of the surface; so far as the erosion, Paget's "eczema," reaches, the epidermis is largely replaced by a mucous membrane-like, actively proliferating epithelium, which, swollen and uncornified, is thrown off as a crust. Only occasionally

and locally do the fibrillated epithelial cells get the mastery, and there developes a drier, firmer and better cornified upper layer, in which very numerous, half-œdematous, "encysted," vesicular epithelial cells are found. The diminished resistance of the horny covering * explains how it is that, in spite of the abundance of mitosis, the inter-papillary ridge system does not penetrate into the cutis, as it does in psoriasis and eczema.

If we review the changes just described, we see that the process has not the slightest resemblance to the ordinary cutaneous catarrhs, especially Eczema and Psoriasis. We have here not an ordinary cellular œdema, but a metaplasia of the epithelial cells; these are converted into fibreless, more movable epithelial cells, which swell up into œdematous lumps, which, no longer undergoing cornification, and loosely placed one on the other, are constantly thrown off. A certain resemblance exists between the loss of fibres and the falling asunder of the epithelial cells, on the one hand with Darier's disease (conf. the spaces in the epithelium itself), and on the other with certain commencing cancers (sailor's skin, nævo-carcinoma). What in Darier's disease induces the hyalin swelling of the dry epithelium, is supplied in Paget's by the cellular œdema; in both cases there develope nucleated clumps, without connection with the neighbouring epithelium, in the former, usually, in the latter, rarely, with shell-like surroundings from their own or neighbouring parts of the fibrillary system.

It was therefore no accident that Darier should have stated of these two diseases, that there appeared cell forms which were not epithelial. In both cases, we have a combination of partial disappearance of the epithelial fibrillation and different protoplasmic degenerations, by which the cells are, some of them, converted into spherical vesicles, and deform their neighbours like foreign bodies. The œdematous character of the cells in Paget's disease prevents the appearance of kerato-hyalin, which, in Darier's disease, so clearly establishes the epithelial nature of the cells in question.

After this discussion, I may spare myself a criticism of the works of Darier and Wickham. Their facts correspond perfectly well with our demonstration of the process, without any assumption of psorosperms. I will only note that, so far as concerns the œdematous, non-encysted forms, Karg came to the same conclusion before me, but he did not find the encysted forms in his case. Since the patient whom I examined was the one on whom Karg afterwards operated, I can state that, even there, encysted forms were present, though

* Conf. p. 202. $\text{In.} = \frac{\text{RP. RH.}}{\text{RC.}} \text{Ep.}$ When RH. is minimal, in spite of Ep. being increased, In. cannot be great.

in limited number. In general these forms—for the reasons just given—have been found more rarely than the simple œdematous,* even by Darier and Wickham, in Paget's disease of the breast.

In relation to the accompanying affection of the cutis, I have only one thing to add to Darier's statements, viz.: that the dense, subepithelial, cellular infiltration beneath, on which all authors lay weight, is a pure plasmoma. This band of plasma cells, which completely fills the horizontal plate of the papillary body, and extends more or less widely into the œdematous papillæ, usually leaving their uppermost ends free, is the most exquisite plasmoma conceivable. All the plasma cells are of almost the same size, and show no transitions into paled or giant cells. It recalls the plasmoma which often, for a long time, surrounds the commencement of a cancer, before the rapid ingrowth has begun. We may therefore, with Karg, regard it as a bulwark against the cancerous growth. Its existence alone, would suffice to make the assumption of an eczematous nature of Paget's disease impossible; such a plasmoma is incompatible with an ordinary cutaneous catarrh.

As regards the cancerous development in Paget's disease, I can confirm the general statement, that there are different forms and points of development. Sometimes it begins on the surface epithelium, sometimes in the lactiferous ducts, sometimes in the breast itself; it is usually of the large or small alveolar form, more rarely of the reticular. This mainly depends on whether the growth proceeds from the glands, from the already affected surface, or from parts of the surface or ducts, still clothed with normal epithelium. In one piece from my patient, it developed from an, as yet, unaltered part of the surface epithelium, and was consequently coarsely reticular. But Karg figures, from the same patient, the commencement of an alveolar growth, on the basis of an affected part of the surface epithelium. Through the kindness of Sir James Paget, I obtained several pieces of Paget's disease, which had been a long time in spirit. In one of them could be seen the origin of the cancer from the milk ducts, in another, of the small alveolar form, from the affected surface. In two other cases the origin was indefinite; one of the cases was a small alveolar, the other, partly a large alveolar cancer, partly a cancerous lymphatic infarction.

I cannot therefore, of Paget's disease of the breast, any more than of sailor's skin and Xeroderma pigmentosum, admit a direct transition of the skin disease into cancer, and I find myself here in contradiction to Karg, who regards the affection of the surface epithelium as already a superficial cancer. To me, this affection of the surface is unique,

* Wickham found them in abundance in a case of Paget's disease in a man (scrotum).

and as different from cancer as from eczema, and it leads, as the French writers note, not directly and necessarily to cancer, but it prepares the ground for it so successfully, that, in most cases, cancer developes.

This preparation of the ground probably partly depends on the loss of the epithelial fibrillation, as in Xeroderma pigmentosum and in nævo-carcinoma; but this alone does not suffice to explain the cancerous epithelial growth.

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6. *Nævo- and Melano-carcinoma.*

Since the melano-carcinomata of the skin always take their origin in pigmented moles, and, on the other hand, there can hardly be nævo-carcinomata, completely without pigment, it is as well to describe together those two groups of tumours, which are combined by gradual transitions. And further, in every other aspect, the character of the two is the same. In all cases we are dealing with rapidly growing, pigmented carcinomata, of alveolar structure, which soon lead to infection of the lymphatic glands, to more or less melanotic metastasis and a fatal termination.

The well-known origin of these tumours explains their connection. They develope from flat, always pigmented, or elevated, more or less pigmented, rarely absolutely unpigmented soft nævi. The more the latter have the type of simple soft warts, the more evident is the cellular, medullary character of the carcinomata; the more the pigment predominates, the more do the primary and secondary growths represent true melanomata. But the basis even of the latter is formed by melanotic epithelium, and in the blackest nodules there are found a few unpigmented spots, in which the epithelial character and the alveolar formation is distinct. The pigment has evidently a favouring effect on the epithelial growth and extension; the more pigmented the nævus, the more active is the growth and deleterious the

action of the new formation. We see the same thing in the soft nævi, where also the pigment, if in quantity, leads to metamorphosis of the epithelium and a-typical growth, and we often see there, that the cellular processes commence with a local collection of pigment.

From the fact noted in describing nævi, that the well-known cellular cords of soft nævi consist of true epidermic epithelium, which has been snared off from the surface epithelium in the embryonic period or in early youth, the development of cancer from them is quite comprehensible, indeed self-evident. This fundamental fact supplies the best possible basis for Cohnheim's theory of certain carcinomata, a foundation more certain than Cohnheim himself was able to supply. While Cohnheim's theory, which derived most tumours from stranded embryonic germs, is recognised and adopted for many benign tumours (Syringadenoma, Dermoid, Atheroma, etc.), it met much opposition in the explanation of the malignant tumours, especially the carcinomata, and in the present infectious epoch finds few supporters. On the one hand, it compels us to ascribe the malignity to the simple predominance of certain, otherwise physiological collections of cells. The extension, the carcinomatous type, may be the simple result of the absence of resistance of the mesoderm, but the deleterious general effect is incomprehensible without something foreign from without—in short, something parasitic. But, on the other hand, a superfluous germ, as the nucleus of a later tumour, is nowhere less likely than on the surface epithelium, where a constant renewal and separation goes on, which would undoubtedly very rapidly get rid of Cohnheim's superfluous cell groups. Even if we were in a condition (which I believe we are) to distinguish embryonic epithelium from that of adults, a search for it in the surface epithelium would be a sisyphean task. Embryonic epithelial germs which have been separated from the surface epithelium, could only be conceived and expected in the connective tissue. Consequently all carcinomata which proceed from the surface—and they are by far the most numerous—have no possible prospect of being regarded, in Cohnheim's sense, on histological investigation, as "a-typical new growths of embryonic origin."

It is very significant that those truly malignant cancers, which are to us most important and interesting, those whose previous history we know most thoroughly, viz., the carcinomata on the basis of other dermatoses and affections of the mucous membrane (Rodent ulcer, paraffin cancer, etc.), were not recognised by Cohnheim as true cancers. He consequently directs us, on the skin, to those whose origin is known neither clinically nor histologically, or at least not so distinctly as to point to their external origin.

It is an instance of the irony of fate, that among those latter there

is a well-characterised group, which astonishingly fills all the postulates which Cohnheim laid down for his carcinomata, and all unknown to him, since, on the one hand, they were mostly regarded as belonging to the sarcomata, and on the other, the epithelial nature of their *matrix* was unknown. In the soft nævi we have before us a true and easily recognisable epithelial tissue, which, in embryonic life (or in early infancy), has been deposited, as a superfluous germ, in the connective tissue, and has preserved its independence. And we see, from reasons unknown to us, but exactly as Cohnheim suggests, these sleeping germs wake up to a new life, and develope into the most malignant of all tumours. Had he been still alive, Cohnheim would certainly have regarded this process as a most important confirmation of his theory, but he would have had to convince himself, that only one single group of carcinomata, the nævo- and melano-carcinomata, complied with it. And even this group, the supporters of the parasitic theory may utilise, for in this slumbering epithelial deposit there must develope something foreign, in order to make it carcinomatous; most nævi only become malignant after injury. Then this true Cohnheim's germ would only be—the suitable soil.

The recognition of the primary, benign stage, which Cohnheim regarded as so incomprehensible in carcinoma, although he assumed it as a necessary preliminary for every malignant tumour, is more easy in the nævo-carcinomata than anywhere else. One has only to consider the whole history of soft nævi. We find that the first a-typical growth of the surface epithelium, which, usually with the assistance of a great amount of pigment, leads to the formation of the nævi, recalls very much the later appearances of melanotic cancers. In the interval, this progressive disturbance of nutrition of the epithelium is at rest. The epithelial germs are snared off from the surface, and remain dormant, in small and large groups, in the connective tissue of the upper cutis. A series of mechanical changes may take place; arrangement of the epithelium in rows, snaring off of the growth, with compression of the deeper lying areas, extension of the superficial alveolæ; ultimately, the stagnation œdema may lead to the degeneration and disappearance of the enclosed epithelial masses; or new, peripheral epithelial growths give the tumour the shape of a bramble. During all these changes the embryonic epithelium remains passive, but it may take on active growth, and then there immediately develope, in the connective tissue of the cutis, cancerous areas, whose alveolar structure is innate in them, and persists.

I have a number of pigmented nævo-carcinomata of the skin, two from the face, two from the back, and two metastatic melano-carcinomata of the hypoderm, which had developed from pigmented nævo-

carcinomata. All show the same alveolar type and the same relation between epithelium and pigment. The following description is chiefly taken from a faintly pigmented nævo-carcinoma, half the size of an apple, which I owe to the kindness of Dr E. Fraenkel. In it there were parts of pretty much unaltered nævus, and others of primary nævo-carcinoma, which, in the definiteness of their origin, left nothing to be desired. In the most peripheral sections, on specially considering the intra-cutaneous epithelial processes of the swollen nævus, we get the impression of an ordinary, finely-striped or feathered, soft "mother's mark," in a condition of œdema. The connective tissue, which separates the surface epithelium from the cutaneous epithelial processes, is especially œdematous; the epithelial alveoli, here, are swollen, rounded and loosened; some of their cells have fallen out. But a very notable change has taken place in the finer connective tissue processes, which separate the epithelial processes; there is a considerable collection of plasma cells and a moderate increase of mast cells. These scattered collections of large plasma cells run together, underneath the nævus, into a small, continuous zone of plasma cells, and this extends further into the surroundings of the nævus, which externally appear healthy, but histologically show enlargement of the epithelial ridges, and the presence of nævus epithelium in the papillæ. Indeed the sub-papillary plasmoma is, here at the periphery, more developed than under the nævus itself, so that this zone, which is quite free from carcinoma, and only contains the terminal extensions of the nævus, looks like an independent affection, something like an infective granuloma. But it corresponds, with its epithelial growth and its plasma cells, only to the peripheral zone of homologous progressive disturbance of nutrition, so frequent in carcinoma.

A little further, and the sections show the first carcinomatous change. The great mass of the nævus epithelium is still inactive, but some of the epithelial processes at the upper and under margin are widened, the individual cells in them loosened and partly fallen out, and from them, surrounded and permeated by plasma cells, processes extend into the tissue. These processes, of the small alveolar type, show exactly the same clear, round or cubical, large nucleated epithelial cells, as the swollen alveoli of the nævus from which they come. But there also appear a few larger epithelial nests, which are certainly formed from the same closely packed, cubical epithelial cells, without the interposition of connective tissue. A very large area of this nature, at the under margin of the nævus, is as large as a mustard seed, and therefore visible to the naked eye. Finally there are found, even on the otherwise quite inactive surface epithelium, a few buds, which pass directly into nævus epithelial nests, usually immediately

lose their hard, prickle character, and are transformed into the type of mucous membrane epithelium, or better, of glandular epithelium, seen in nævus epithelia and alveolar carcinoma.

Still further towards the centre of the tumour, all the nævus alveoli have undergone carcinomatous degeneration, without the surface epithelium taking part, as a whole, in the proliferation. Some of the nævus epithelia have enlarged to twice or four times their ordinary size, and are undergoing regular mitosis. They are cubical, pale, pretty homogeneous cells, with regular oval nuclei, four or six in a cell. The cells have a fine, frothy, never coarsely fibrillated structure, and are consequently only loosely connected. On fine sections, many individual cells and often a great part of the contents fall out. Where the inter-alveolar, plasmomatic new formation is small, the alveoli grow to a considerable size, and compress one another and the surface epithelium, whose processes pass into the interior of the tumour. But where the plasmomatic formation is considerable, therefore especially at the under margin of the tumour, the large alveoli break up into a quantity of smaller ones; there is a widespread scattering of the epithelium.

The melanotic pigment, which, in the still unchanged nævus in this case, is only sparingly developed, and covers little but the apices of the nævus processes in the sub-papillary tissue, without penetrating them in any quantity, now begins to multiply. But it is still limited almost entirely to the connective tissue septa, and lies here in the form of brown granules and clumps, free or in spindle cells, and occasionally in plasma cells. Only rarely does it invade the nævus epithelium, which otherwise shows no change in its relation to its surroundings.

The plasmoma tissue now and again attains greater dimensions, but it is always irregularly distributed inside the carcinoma. In some places it is converted, by the disappearance of the plasma cells and the multiplication of the very much enlarged spindle cells and the collagen, into a firm fibromatous tissue. Mast cells are rare.

The carcinoma culminates exactly in the centre of the tumour. We may here distinguish three segments; an outer necrotic zone, one to two millimetres broad, occasionally containing different bacteria, a central one about five millimetres broad, less stained, and an equally broad, undermost, darkly stained zone. In the lowest segment, next the subcutaneous tissue, the cancer has the alveolar form just described. The cells are pretty equal in size. The cancer nests have here wormed their way into the plasmomatic and fibromatous tissue.

But there are greater changes in the middle zone. The cancerous epithelial cells are here swollen to an enormous size, and thus the

alveolar structure is lost; the individual epithelial cells are free, grow and proliferate in all possible directions, and irregularly fill the spaces between the dilated capillaries, being separated and permeated by a few connective tissue processes. 20-25μ is the ordinary size of the cubical or round cells, 20-30μ that of the oval ones; enormous ones of 40-60μ are no rarity; some cell giants may grow to a size of 60-80μ, or, under lateral pressure, to a size of 40-100μ, into colossal, epi-

FIG. 28.—Alveolar Nævo-carcinoma.

A. Cancerous Alveoli. *N*. Necrotic zone. *Sp*. Large, spindle-shaped epithelial cells. *G*. Epithelial giant cells.

thelial spindle cells, which one at first scarcely recognises as epithelial. The nucleus increases proportionately to the cell. But in addition, there may develope multi-nuclear cells, and later on true giant cells, which have the most varied forms, and ten to fifty or more nuclei. These nuclei never lie, as in tubercular giant cells, concentrically, but are either regularly distributed, or more or less collected on one side of the cell; the protoplasm is, further, never difficult to stain; indeed, with a protoplasm stain, it stains deeper than the rest of the epithelium, so that these "epithelio-plaques" stand out, even with a low power. Their form is indescribable, for no one resembles another;

many are cubical or round, but most of them show all sorts of bendings and processes. Usually, several of them lie together, in the centre of a collection of especially large cancer cells.

The nuclei of the large cells and the giant cells frequently contain vacuoles of considerable size, which sometimes distend the nucleus to a simple bleb. The ordinary degenerations of the protoplasm, which distinguish the fungating cancers, are, in spite of the great swelling of the protoplasm, sought for in vain. In particular, hyalin degeneration, with its remarkable products, is not present, which is an argument in favour of the fact, that it mainly affects the system of fibres, which is here absent. With a good acid fuchsin-picric stain, there appear, only outside the epithelium, immediately around the blood vessels, specific, red-stained clumps and balls, partly free in collections of small sphericles, partly enclosed in cells, perhaps leucocytes. Since, as with this stain, partially dried red blood corpuscles stain like hyalin, it is not impossible that these may be metamorphosed erythrocytes.

The pigment is, at the height of development, only present in moderate degree, in broad streaks in the middle zone. It is here mainly inter-cellular, in the few spindle cells along the blood vessels, more abundantly in the epithelial cells, nor does it spare the "epithelio-plaques."

All the appearances described in the centre of the ulcerated tumour: the mono-nuclear, multi-nuclear cell giants and giant cells, arranged in alveoli, enclosed in connective tissue rich in plasma cells, are found repeated in the carcinomatous lymphatic glands. Even the pigment is present in the same moderate degree, partly in the cellular connective tissue septa, partly in the epithelial cells of the alveoli.

The second case, of nævo-carcinoma of the back, corresponds, in the main, with that just described. Only the epithelial processes do not show the same active swelling of the individual cells, but rather a tendency to partial liquefaction, so that the same alveoli present cystoid and tubular excavations. The pigment is more abundant, but still in lines, and in very varying quantity. Where it is most dense, the epithelial cells show the commencement of granular degeneration and necrosis.

An exact reproduction of the first case was found in a third, a flat, very faintly pigmented nævo-carcinoma of the skin of the face. The alveoli and the individual cells did not reach the same enormous size, and there was no formation of epithelial giant cells. The pigment was limited to the surface, between the epithelial covering and the proliferating cords of nævus epithelium, and the growth had reached no further than the neighbourhood of the coil glands. Plasma cells were only present in small numbers at the margin of the tumour.

Here also, there was vacuolisation of the nuclei, but no other degeneration of the epithelium.

My last case of primary nævo-carcinoma is very deeply pigmented, and consequently represents a so-called melanoma. Where the pigment is more sparing, appropriate staining distinctly shows the alveolar arrangement, for at these places it is mainly the connective tissue septa which are pigmented. And the pigment is always first and mainly present outside the tumour cells proper; just as in the pigmented nævi, it is mainly found around the epithelial processes in the cutis.

The two metastatic melano-carcinomata of the hypoderm have a special interest, since they were labelled with the diagnosis, metastatic melano-sarcoma. Since the one was demonstrably due to a pigmented mother's mark, and the malignant tumours of mother's marks are all carcinomata, the diagnosis of metastatic nodules as sarcomata, should always be very cautiously made. The frequent references, in literature, to such cases as generalised sarcomata—even after histological investigation—depends mainly on an error. I can, supported by only two, afterwards explained cases, express myself pretty positively in this connection, for here the mistake was very natural. For, to note at once this important point, the simultaneous severe pigmentation makes, not only the differentiation of the principal cells more difficult, but still more that of the connective tissue cells around the tumour cells, and therefore the genesis of the latter. As is evident from the description of the primary nævo-carcinomata, the pigmentation is a completely independent factor, which complicates, in greater or less degree, almost all nævo-carcinomata. Only rarely is the pigmentation so severe, that the name melanoma may be applied to the primary tumour. But since the melanosis makes the primary tumour more malignant, and secondary cutaneous nodules are only found in the more severely pigmented primary cases, the metastatic nodules of the hypoderm are always exceptionally rich in pigment.

> They are seated, firmly encapsuled, in the subcutaneous tissue, are of the size of cherry stones, cherries or small apples; they thin the cutis over them, and before rupturing, shine through, bluish, then bluish-black and finally coal-black, and show on section a brown or brownish-black colour. The surroundings are perfectly healthy; the nodules show no diffuse infiltration and no pigmented scattered processes; they lie, sharply defined, with their deep brown colour, in the white tissue, like Bohemian garnets in slate. Their appearance is accompanied by melanuria and melanæmia, and, after the rupture of the softened nodules, there constantly exudes a black, inky fluid, mixed with tissue debris. The cases soon terminate fatally, with metastases in the lymph glands, liver, heart, intestine, muscles, cerebral membranes, etc.

In my first case, the nodules, which had the colour of brown coal,

consisted of small, densely-packed epithelia, about the size of liver cells, lying together in long alveoli, and separated by very fine, thinly-scattered collagenous fibres. They occupied the place of the original fat lobules, and, without penetrating between the fat cells of the neighbourhood, had pushed them in a straight line before them, and thus formed a firm capsule, from the surrounding tissue of the hypoderm and the completely unaffected, elevated cutis. Where larger connective tissue septa penetrated into the nodules, they introduced a large amount of pigment, which extended into the epithelial mass on all sides. The macroscopically homogeneous colour was seen to consist, microscopically, of a brown reticulum, corresponding to the original vessels. Wherever the epithelium was heavily laden with pigment, it was partly necrotic, showed a very faint or no nuclear stain, and was converted into shapeless, pigmentary debris. The connective tissue septa, on the other hand, withstood the densest pigmentation of their cells, without breaking down.

After my first case—as was to be expected—had proved to be a melanotic carcinoma, I endeavoured to procure material from some published case of melano-sarcoma, which had been carefully examined, both clinically and histologically, and in this, through the kindness of Professor M'Call Anderson, I was successful.*

Nothing was left of the primary tumour, which developed from a pigmented mole on the arm, but I received secondary nodules of the hypoderm, the muscles, the intestines, and the brain. The nodules of the subcutaneous tissue were, like all the others, and according to the description of the authors, round, and sharply marked off from the surroundings, like little masses of coal. Consequently the investigation of the very deeply pigmented tumour cells was very difficult. Only after long treatment in alkali, with H_2O_2 and Chlorine water, were the sections so far bleached that powerful nuclear and protoplasmic stains were partially successful, and then we had exactly the same appearances as in the preceding case; small, densely compressed alveoli, enclosed by very little connecting substance, filled with relatively small mono-nuclear, and only occasionally with larger multi-nuclear epithelia, which, with few exceptions, contained deep brown pigment. Great stretches of the cutaneous nodule could no longer be analysed into cells, but consisted of pigmented cellular debris, with a few free nuclei.

Still more instructive were the scattered, smaller, muscular carcinomata. Here, much more distinctly than in the cutaneous nodules, is seen the complete independence of the extension of the pigment, of that of the epithelium. The muscular bundles are compressed and destroyed by the epithelial masses, but these do not penetrate between

* Tennent's case, Glasgow Med. Journ., 1885, August.

them. But the pigment precedes the epithelium, and nestles between the still healthy muscular bundles around, applying itself to the muscular nuclei, and the scattered connective tissue nuclei. This is still more distinct in the carcinomatous nodules of the cortex cerebri, which penetrated widely into it, from the deeply pigmented pia. They were surrounded by a small zone of immigrated pigment, which lay partly free in the neuroglia and partly collected in the ganglia.

Naturally, in all connective tissue organs, these outposts of more movable pigment induce an external zone of more or less pigmented connective tissue cells, and thus suggest the view that the succeeding pigmented tumour cells develope from these pigmented connective tissue cells. Such an error is all the more easy, since the epithelial nature of the tumour cells, and their alveolar arrangement, is not evident without artificial bleaching agents. In the less pigmented primary carcinomata such a mistake is more easy to avoid. At all events we have sufficient grounds for adopting, in future, a sceptical attitude to the diagnosis of metastatic melanotic sarcoma. The epithelial processes of soft nævi, the alveolar nævo-carcinomata, and the melanotic, metastatic carcinomata of the hypoderm, form such a regular sequence, that departures from this ordinary process must be very clearly defined.

(β). *Sarcoma.*

The sarcomata of the skin have only recently attracted attention, and in particular, the relative frequency of primary, *i.e.*, cutaneous sarcomata proper, has only recently been recognised. If we reckon with them all solitary sarcomatous nodules, they are much more frequent than cutaneous metastasis in the sarcomata of the internal organs.

They fall into the two great groups, of solitary and multiple sarcomata. A sarcoma is solitary, if it persist for a long time, occasionally tens of years, as a uniform nodule, without changes other than simple increase in size, or ulceration. It represents, so far, an innocent affection, completely curable by thorough extirpation. In many cases, regional or universal metastases of the skin or internal organs follow solitary sarcoma. The solitary sarcomata are usually not melanotic, though darkly coloured, reddish, bluish red to black, now and again transparent, of the size of a pea to a cherry, and are seated preferentially on the face (cheeks, eyelids), the feet and hands, or on other parts of the extremities, more rarely on the trunk. They are partly compressible, bleed readily and severely when of the nature of angio-sarcomata, or they are more consistent, fusocellular- or fibro-sarcomata. The long persisting, solitary sarcomata resemble in structure the infective granulomata rather than the ordinary sarcomata.

The metastases of the solitary nodules are usually hypodermal and pigmented, at first regional, later universal.

Many tumours developed from pigmented nævi have been described as solitary melanotic sarcoma. Since the pigmented nævi invariably lead to melanotic carcinoma and carcinomatous metastases (which see), such cases are always to be accepted with caution, although I by no means deny the occurrence of melanotic sarcomata of the skin.

The great group of *multiple sarcomata* comprises all those cases, which, without any pre-existing mother growth, show, either regionally (an arm, a leg, the face) or symmetrically (both legs, trunk), and practically simultaneously, a number of individual tumours, so that a uniform development must be assumed for all. They are best divided into *dermal* and *hypodermal* multiple sarcomata.

The dermal may be divided, from their histological formation and external type, into four distinct forms.

1. *Sarcoma multiplex cutaneum durum album.*
(Two cases of my own.)

This is the simplest form. It consists of firm, white or yellowish, more rarely light red or bluish, but *always pale, well-defined nodules, in the cutis itself*, of the size of peas, cherries or plums. These in time project, owing to the elastic pressure of the skin, they are "born," and ultimately become pedunculated; now and again they drop off (spontaneous healing). This fungus-like snaring off is frequently accompanied by a partial softening of the nodule, which is, however, always superficial, and never leads to the laxity of a fibroma molluscum; though sarcoma cases have most resemblance to this disease. But the tumours do not develope on pre-existing nævi. The surface is tense, smooth, later partly thrown off; now and then teleangiectases are found on it. The tumours are indolent, may be slightly compressed without pain, and show no tendency to pigmentation, ulceration or disappearance. They are regularly distributed all over the body, especially on the trunk, but are also present on the head, and only absent on the palms and soles. They develope slowly in the course of several years, and only ultimately lead to marasmus. My two cases were both women, and the tumours were *fusocellular*- and fibro-sarcomata.

2. *Sarcoma multiplex cutaneum durum pigmentosum* (*Typus Piffard*).

This usually resembles the preceding form, only the nodules are more or less dark, bluish-red to brownish-red, and, on section, are yellowish, with dark brown spots. They are often regionally limited,

especially to the under half of the body, and are then especially characteristic. Very characteristic is the preliminary stage of many nodules, in the form of teleangiectases, the size of beans, mixed with hæmorrhages, which do not always go on to nodules, but are frequently converted into pigmented spots. The consistence of the nodules is firm, but they are not so hard as in the preceding case; they yield to prolonged pressure. When wounded, they bleed severely and long. Their brown colour has often led to confusion with melanotic carcinomata (so-called melano-sarcoma*), from which they must be clearly distinguished; they are not preceded by melanotic nævi. They are *fusocellular-angio-* and *angiofibro-sarcomata.* (There is an excellent illustration in Piffard's Photographic Atlas, plate 20.)

3. *Sarcoma multiplex cutaneum molle* (*Typus Neumann*).

This form of sarcoma developes from nodular *infiltrations*, which permeate the skin of the hypoderm, in the form of rounded or circularly arranged plates, and swell up to broad-based, lobulated tumours, frequently of great size. The consistence is soft, the colour, pale yellowish or red; they especially affect the trunk. There is a certain resemblance to Mycosis fungoides, but the position of the tumours is, from the commencement, deep, there are none of the eczematous, epidermic changes of that disease, and the sarcomatous tumours do not spontaneously disappear. Histologically, they are round-celled sarcomata. (Illustrations: Neumann's Atlas, plate 63; Morrow's Atlas, plate 68, fig. 1.)

4. *Sarcoma multiplex cutaneum gummatodes* (*Typus Funk-Hyde*).

This sarcoma is, like the preceding one, soft, and little or not at all pigmented. The nodules rapidly reach a considerable size, and have the peculiarity that, when they reach a certain size, they invariably soften in the centre, and, after discharging a gummatous, semi-solid debris, collapse. They are fusocellular or coarse cellular sarcomata, with myxomatous central softening. (Illustration: Morrow's Atlas, plate 68, fig. 2.)

These four types of dermal sarcomata have all in common, that they are irregularly scattered over the body, and do not appear in regular sequence. In this they differ from a fifth type, whose main distinction is the systematic extension, from the ends of the extremities, inwards. In the first forms, the absence of a systematic localisation points to a certain indifference of the matrix; in this,

* *e.g.* case of Rothacker and Thompson. Medical News, 1885.

there are evidently predisposing local causes for the special localisation.

5. *Acrosarcoma multiplex cutaneum telcangiectodes (Hebra-Kaposi).*

This first group of *systematised* sarcomata—perhaps in the others only their law of formation is still unknown to us—appears in the form of very dark, blue to bluish-black nodules, on the hands and feet, especially on the fingers, toes, and the sole of the foot. The fingers are thickened and deformed. At the ends of the extremities the nodules run together, and form a painful diffuse infiltration. Then there appear, on the arms and legs, advancing centripetally, at the same time, on the face and genitals, and later, singly, on the trunk, isolated nodules, partly dermal, partly hypodermal, the former light reddish-brown, the latter dark and blue. With extension to the mucous membrane, especially of the large intestine, fever and marasmus, this form leads, more rapidly than the others, to death (Illustration in Hebra's Atlas, Vol. X., plate 9). These sarcomata are fusocellular- or angio-sarcomata, and show abundant pigmentation.

The *hypodermal* sarcomata are either proper to the skin, primary, or they are metastatic nodules. The former constitute a peculiar, very rare type of globocellular tumour, which, beginning in the hypoderm, unites with the cutis, causing wine-red discoloration, is not pigmented, and attains a considerable size. (Perrin's type.)

Much more frequent are the *metastatic nodules of the hypoderm*, spread over the whole body. They are usually well-defined, rounded, irregularly pigmented, hæmorrhagic tumours, which gradually unite with the cutis, project as dark, bluish-brown nodular tumours, and finally ulcerate. In a certain sense, the later nodules, appearing in distant regions in primary multiple cutaneous sarcomatosis, come under this heading, and therefore this group forms a complete clinical and anatomical type. All forms are found: globo-, fusocellular, angiomatous and fibromatous sarcomata. How far this is due to the original tumour, and how far to the site of the daughter tumours, is an interesting question for future investigation.

The hypodermal, melanotic, secondary growths are usually carcinomata (whether they are all so, is still questionable), and must not be confused with hypodermal pigmented teleangiectatic sarcomata. This short survey of the clinical forms shows us, that the difference in the elements of cutaneous sarcomata is not particularly marked. Very rare is the giant cell sarcoma, which is so frequent in the sarcomata of the bones, but, as we shall see, giant cells may occur, though only in a special form of sarcoma of the skin. And the myxo-sarcomata, in

spite of the text-books, appear to be very rare. The most common of the cutaneous sarcomata is the *fusocellular*, with the two varieties of *fibro-* and *angio-sarcomata.* In the hypoderm, the round-celled sarcomata predominate, but they also occur in the cutis proper. We may determine their fusocellular or globocellular character, as well as the amount of fibrillary connective tissue, from their firm or soft character ; the amount of their blood vessels, from the deep red colour and a certain degree of compressibility ; the amount of pigment, from the very deep blue to bluish-black colour ; soft spots on firm nodules point to œdematous or mucous softening, and to future suppuration of the nodules. So that one may form an idea of the structure of the cutaneous sarcomata, without histological investigation. As yet, our clinical and anatomical knowledge of cutaneous sarcomata is not sufficient to enable us to lay down definite histological data for each of these types. Only some of them are formed on such definite bases. Abandoning this endeavour, we must therefore content ourselves with describing the sarcomata of the skin from the forms of the individual cells, and with pointing, here and there, to the relations to clinical appearances. We commence with the

Spindle-celled Sarcoma.

This represents the main type of sarcoma of the cutis proper, since the spindle cells repeat the normal type of the connective tissue cells of the skin of adults. The firm collagenous scaffolding of the latter evidently predisposes to this form of cell, and new formation of fibrillary tissue often goes on alongside that of spindle cells. Only very rarely does the epithelium of the capillaries proliferate independently. We have further to add to the *fusocellular* simple sarcomata, the *fusocellular fibro-* and *angio-sarcomata.*

The genesis of the spindle-celled sarcoma can, of course, only be studied on those cases, where it extends continuously into the skin, and the healthy surroundings are infected by sarcoma cells, for interstitial and encapsuled nodules show less distinct appearances. We see then, corresponding to the transitional zone, a dilatation of the larger blood vessels and all the capillaries in the zone, but no new formation of capillaries, so that in this form a primary angiomatous stage (Babes) is excluded. But since, in the dilatation of the blood vessels, especially of the veins and capillaries, abnormal conditions of transudation are provided, we see in some sarcomata, abundant golden-yellow blood pigment deposited in the adventitial lymph spaces, around the dilated vessels. Our interest is of course especially attracted to the form of the cells, which surround these dilated peripheral vessels. The most

peripheral capillaries show only a swelling of the pre-existing endothelia and immediately adjacent spindle cells, and an enlargement of nuclei and cells, previously scarcely visible. We often see bi-nucleated spindle cells, but never mitosis. Nearer the margin of the tumour, we find the same process of swelling and amitotic division of the cells, accompanying the blood vessels, over a wide area, and it is now also evident in the spaces between the vessels. In spite of the dilatation of the vessels, emigration of leucocytes is very exceptional; there is nothing to point to the origin of the sarcoma cells from them. No new formation of collagenous tissue takes place in this peripheral zone, nor is there any running together of the collagenous or elastic tissue.

This is the form of the outmost periphery of all the extending fusocellular sarcomata of the skin, which I have examined (seven cases). Closer to the actual, even macroscopically visible margin of the tumour, the appearances vary in different cases. In some of them the transition is gradual, new spindle cells simply pushing themselves between the old ones, separating the collagenous bundles and splitting them up, by the development of spindle cells, into finer bundles, and finally into very thin, long fibres. The process of cellular division is difficult to follow, for, even here at the margin, there are no mitoses. Most of the multi-nuclear spindles and recently divided, rounder cells, with round nuclei, are found immediately around the vessels, which are narrowed by the commencing new formation. These rounded, closely packed cells are not to be confounded with leucocytes; in these stealthily advancing nodules, emigration is almost never seen.

In other (three) cases of fusocellular sarcoma, which I have examined, there is a *marginal zone*, characterised by striking appearances. Here the blood vessels, especially the veins, are very greatly dilated, and surrounded, instead of by spindle cells, by a mantle of more rounded cells, which, with a nuclear stain, resembles a leucocytic wall. But a good protoplasm stain shows that these cells are connective tissue cells, and have developed from the rapid division of spindle cells. Four to six cells, lying in a row, often correspond to a large spindle cell, lying parallel to them. Klebs has already described this appearance in the sarcomata. But the most striking appearance, which we never find in perfect spindle-celled sarcoma, is the presence of a few *plasma cells*, scattered irregularly between the round cells. Certainly these are not very large, and have partly lost their coarse granular protoplasm. But the deep specific stain of their protoplasm, their size and their tendency to cubical form, distinctly characterise them as plasma cells. Of course they have, here at the margin of the sarcoma nodule, only a transient existence. Many of them show the

familiar nibbled form of the dissolving ones (*e.g.*, of the healing syphilitic papule, of Ulerythema centrifugum, of Mycosis fungoides, etc.), or they show plasma granulation, only here and there, in a coarse, frothy, clear protoplasm. And we find forms intermediate between these plasma cells and the swollen spindle cells, in spindle-formed cells which show central swelling and plasma granulation.

But both the round or cubical daughter cells of the spindle cells, and the short-lived, single plasma cells are only to be regarded as introductory to the luxuriant cell proliferation and cell nutrition at the vascular periphery of the spindle-celled sarcoma; into the tumour proper they do not enter. Only in one case have I found, at some distance from the tumour, scattered plasma cells and small areas of them, such as are constantly present in the surroundings of the infective granulomata (Syphilis, Tuberculosis, etc.). And the mast cells, which are so abundantly present in all granulomata, are almost completely absent around the fusocellular sarcoma, and inside it entirely so.

Whether surrounded by a special marginal zone or not, the fully formed, fusocellular cutaneous sarcoma is a tissue of very homogeneous formation. Closely-packed spindle cells, arranged in parallel bundles, sheath the narrowed vessels; they grow along inside all the collagenous bundles, which they cause to disappear, and substitute, and they accompany, in the form of hollow cylinders or plates, all the enclosed organs of the skin, which, if diminished, undergo atrophy, like the hair follicles, or are often only elongated and unrolled, like the coil glands. The masses of spindle cells then grow through the septa of the fatty tissue, and attack, without reaction, one lobule after another; now and again we find the region of the original panniculus still indicated by a few well-preserved fat cells. In addition to the blood vessels, only the smooth muscular bundles, which are notoriously like sarcoma spindles with a simple nuclear stain, appear to be preserved, but with a proper water-blue-eosin or water-blue-orcein stain they are easily distinguished from them. The elastic tissue perishes at once, even in the transitional zone; only around the vessels are there, here and there, traces of it. The lymphatic system of the skin also suffers in the pure spindle-celled sarcoma, but not in the sense of a complete obliteration (Siegenbeck van Heukelom). With an ordinary nuclear stain, the tissue certainly conveys the impression that it is densely composed of cells, with regular, fine collagenous bundles. But if we demonstrate, by means of a specific collagen stain (water-blue or alkalin-blue), the contours of these connective tissue fibrillary bundles, we see that they are permeated by a system of innumerable, fine, connected spaces; the tissue looks like a fine sponge. But the type of the lymph channels

is altered. The normal spaces of the crossing, thick, collagenous bundles have assumed, with the welding and the splitting up of the collagenous tissue, a fineness like filigree; there is a new, fine canal for every ingrowing spindle cell. One might perhaps expect, with the extension of the process and the consumption of all the collagenous tissue, an obliteration of the lymphatic system. But in the case which I examined, there was always a persisting remnant of collagenous intersubstance, and I must regard its complete disappearance in the skin as doubtful.

To this system of fine lymphatics, corresponds a very distinct system of coarser lymph spaces. But here also an alteration of type is undeniable. Since the growth of new spindle cells at first attacks the open routes of the old blood vessels and collagenous bundles, as the nodule developes, we reach a point, at which the bundles of spindle cells, crossing in all directions, collide, and compress one another. From these bundles, there gradually developes a tissue, of more coarsely-fibrillated, regular formation; many small bundles crossing each other at acute angles are welded together into larger, parallel-fibred bundles. In the centre of these fasciculæ, we usually find a capillary or a large blood vessel. But they are separated from each other by larger, irregular spaces, which must develope by the advancing growth of bundles crossing each other, such as are seen in all fibromata and cord-like granulomata (Neuroleprides). In such spaces are enclosed all those parts which do not share in the sarcomatous change, *e.g.*, the coil glands.

Further, in relation to the more or less distinct fascicular arrangement of the spindle cells, no one case of cutaneous sarcoma exactly resembles another. The same is true of their extension inside the cutaneous tissue. Those which develope spontaneously leave the cutis proper long intact; but gradually this becomes richer in spindle cells, which, especially along the vessels, assume a sarcomatous type, and then combine, in places, with the sarcoma of the hypoderm. In the skin most sarcomata only later attack the papillary body. Usually this and a superficial layer of the cutis remain free from sarcoma, only there also, there is, in places, a greater abundance of cells. In one case of pure spindle-celled sarcoma, I saw the sarcoma tissue everywhere reaching close up to the sub-epithelial margin, which had preserved its normal formation. Most directly connected with the epithelium, is the sarcoma, in those cases where an active dilatation of the vessels, along with luxuriant cell proliferation, marks the advancing border of the tumour. Then we find, here and there, even the still preserved papillary body converted into sarcomatous marginal tissue, with small cubical or round cells and plasma cells.

As to the behaviour of the blood vessels, on which, it appears to me, too much weight has recently been laid, that varies very much. We have already spoken of the occasional active dilatation at the extending margin of the sarcoma. In the interior of the nodules, at the height of development, the blood vessels are, in general, not dilated, but their walls are almost always thickened, and—owing to the immovable, inelastic nodule,—usually gaping. In several cases I have found hyalin, only partially obstructive thrombi in them. The number of blood vessels is not especially great; they seem to have increased in proportion to the growth of the nodule. The relation of arteries and capillaries is also in no way abnormal, but the distribution of the capillaries, corresponding to the more regular form and pressure in the tumour, is more regular than in the normal skin. In the coarse fascicular cases, the capillaries are few, while in the irregularly formed, looser nodules they are more numerous, and in places may be very abundant. But they are always sharply marked off from the spindle cell tissue, and there is nothing to point to a direct transition of the blood vessel walls into sarcoma tissue. The firmer the formation of the nodule, and the more the media of the vessels with its elastic elements has disappeared, the thinner walled and simpler appear the vessels.

But this disappearance of the vessels, as an independent part of the growth, is to be regarded as a true atrophy, and by no means as the sign of a direct and primary passage of the vessels into the tumour. The attribution of all sarcoma cells to vascular perithelium, I must especially contest for the fusocellular sarcomata, and naturally still more that to the endothelium. The first indications of tumour growth are certainly found, here as in almost all progressive changes of the skin, on the perithelium of the capillaries and transitional vessels, but later, the whole of the cells of the cutis share in it. I would make an exception in the fusocellular type, only for the marginal zone of some cases, accompanied by dilatation of the vessels, where, with the budding of the vascular perithelia and endothelia, there is usually a deposit of golden-yellow blood pigment around them.

The best proof, that in these pure fusocellular forms we are not dealing with an angiomatous development of the tumour cells, is supplied by the true fusocellular angio-sarcomata of the skin, and I therefore take up next this mixed form of fusocellular sarcoma. A very beautiful example I owe to Dr E. Fraenkel.

It was a diffuse, spindle-celled sarcoma, with a zone of vascular degeneration, and containing a considerable amount of pigment. In a small segment of the tumour margin proper, the large veins are greatly dilated, as are the capillaries, and these, along with the transitional vessels, are surrounded by cellular mantles, which, on close examina-

tion, are found to consist of rounded, amitotically divided connective tissue cells, with here and there scattered plasma cells between them. Between these outposts and the sarcoma itself, lies a small zone of commencing invasion, which, even with a low power, has a strikingly reticular appearance. In it, all the connective tissue bundles are still well preserved, but some are surrounded by a wreath of young spindle cells, which, with their numerous processes, somewhat resemble "spider" or "winged" cells. Some contain pigment granules, and they give to the zone its reticulated appearance. The few blood capillaries, which run through them, show enlarged endo- and peri-thelia, and their cells are in direct connection with the net of spindle cells; but the small number of these capillaries contradicts the assumption, that all young sarcoma cells are derived from them. The advancing, youngest invasion zone is consequently not angiomatous, but purely sarcomatous.

The conditions are otherwise at the margin of the tumour proper. Here the sarcoma cells form an unusually confused, muddled up tissue. Although when carefully analysed they are seen to be mainly spindle cells, the ordinary parallel, fascicular structure of the fusocellular sarcoma is absent. This is due to a dense net of young blood capillaries, which penetrates the whole nodule in all directions, and takes up the spindle cells in its narrow meshes. These are thus almost all semi-spherically bent, for they are applied with their processes to one or more capillary loops, or surround the few connective tissue rafters, which have been spared by the new growth. We have therefore hardly anywhere, two completely parallel spindle cells. Here we can see, in many places most clearly, how true spindle cells of the tumour directly branch off from the endothelium of small capillaries, and thus represent real, dry, capillary loops, while the dense arrangement of the blood vessels stamps on the tumour cells, as a whole, the peri-thelial character. But there are, further, two circumstances, which show the special relation of this sarcoma to capillary budding. Firstly, almost all the tumour cells contain golden-yellow blood pigment, in fine and coarse granules up to quite coarse lumps. The pigment is found almost exclusively inside the cells, varying in amount from a fine tincture up to an amount which conceals the nucleus and the protoplasm. It has everywhere the light yellow colour of blood pigment, and never a melanotic character. The endothelia of the blood capillaries contain it, as well as the inter-capillary cells, but the latter usually contain the greater amount. This sarcoma may serve as an illustration of a deeply-pigmented, but non-melanotic, cutaneous sarcoma.

The other point is the widespread presence of multi-nuclear cells,

which go on to the formation of large chorio-plaques. These cells, which are not otherwise characteristic of the fusocellular sarcomata of the skin, never contain mitoses, but develope amitotically, from the absence of cellular, with constant nuclear division. Those with two and three nuclei, usually still have long processes; the larger ones, with six and more nuclei, are more rounded, and resemble chorio-plaques elsewhere, with the distinction, that the mass of nuclei always exceeds the amount of protoplasm. There is never any alteration of the protoplasm, as in true giant cells. But the multi-nucleated cells and the chorio-plaques all contain more or less pigment. Very frequently they form small centres, around which the adjacent spindle cells are concentrically arranged. In contrast to the splitting up capillaries, many of the transitional vessels and large blood vessels, inside the tumour, have broad walls, which are sometimes hyalin.

We have thus evidently to do, not with a sarcomatously degenerated angioma, but with a spindle-celled sarcoma, which is distinguished only by the regular participation of the blood capillaries; therefore the name *fusocellular angio-sarcoma* is very appropriate. We have considered this formation in such detail, because it absolutely contradicts the assumption, that all sarcomata of the skin have an angiomatous character (Babes). The simple fusocellular sarcomata of the skin contain as few capillaries as the cutis itself; they are therefore white or yellowish white, while the pigmented angio-sarcomata vary in colour between blue, brown, and black.

The next group is that of the *fusocellular fibro-sarcomata.* Among them we can again distinguish two forms, the *diffuse* and the *fascicular.* The diffuse fibro-sarcomata are united with the pure fusocellular sarcomata through so many transitions, that it is difficult to draw a line between them. The reason is evident. The fusocellular sarcoma developes simply by the deposit of new spindle cells, at first in the old collagenous tissue of the cutis. As this gradually disappears, the pure spindle cell character is more and more evident. Now the mixed form of fibro-sarcoma shows a new formation of fibrous tissue, as well as of spindle cells, which may, under certain circumstances, limit the extension of the spindle cell tissue. At a given place it is not always easy to say, whether the collagenous substance between the spindle cells is the remains of the connective tissue, or a new fibromatous formation; but things become clearer, when we examine larger areas, and pay attention to the relative quantity and position, the tinctorial qualities, and the margin from the healthy tissue. Since even the purest spindle-celled sarcomata of the skin always show some collagenous tissue between the spindles, we can only speak of fibro-sarcomata, when, between two spindles, there is at least twice or thrice their width of

collagenous substance; when the layers are compact, the spindles may stand very close to each other. If the arrangement of the fibrillary bundles is different from the normal arrangement of the cutis, *e.g.* regularly horizontal or regularly wavy, that is a fibro-sarcoma. If the new connective tissue between the spindles is not distinctly in long fibres, but apparently homogeneous or amorphous, good staining (water-blue-orcein) will decide the question. The new formed substance then shows a much more regular, *e.g.* latticed structure, than the old, disappearing connective tissue of the cutis, as it is found at the margin of extending fibro-sarcomata; that is found during resorption, *irregularly* folded.

The relation of the elastic tissue is another very good indicitant. All pure fusocellular sarcomata of the skin are completely free from elastin; the elastic fibres disappear everywhere, as the spindles grow in. Where, on the contrary, collagenous tissue persists and multiplies, the elastic tissue does not necessarily perish, and indicates very clearly the limits and quantity of the fibrous tissue in the tumour. I have, for example, a fibro-sarcoma of the umbilical region, in which areas of pure fusocellular sarcoma alternate with those of fibro-sarcoma. In the latter, the elastic fibres are preserved, and a good elastin stain clearly shows the margin of the fusocellular part of the tumour, in which only rudiments of elastic tissue are to be found.

The more fibromatous tissue is present along with the sarcomatous, the simpler is, of course, the diagnosis of the fibro-sarcoma, and it is quite clear in the cases where the fibromatous tissue is in excess. These form the second group of fibro-sarcomata, the *fascicular*. But it is not only the quantity of collagenous tissue, which distinguishes this form of sarcoma, but mainly the separation of fibroma and sarcoma, whose processes wind around and through each other. Thus these tumours have, on superficial consideration, an appearance similar to the fibrous cancers of the skin, especially to Rodent ulcer. But the complete absence of true epithelial cells, the want of connection with epithelial structures, and the transition of the spindles in the sarcoma cords into the purely fusocellular tissue of the tumour, establish the correct diagnosis. Usually the fascicular fibro-sarcomata are irregularly composed in their different parts. Where the fibroma predominates, the sarcomatous processes are small, much swollen and notched, and their spindles are arranged densely and in parallel rows. Where the fibroma is less, the fusocellular cords are broader, more club-like, less separated from the surrounding tissue, and their spindles are not so dense and parallel; but even these processes only take up fibrous tissue between the spindles, and the fascicular character is here well preserved.

At the margin of such sarcomata, we see that their double nature is present from the commencement. The very first cords of sarcomatous spindles are sheathed and separated by firm fibrous cords. Now since these usually contain small vessels and capillaries, it is very probable that, in the interior of these sarcomata, the cellular cords mainly correspond to open (or obliterated) blood vessels, and their immediate surroundings. They would then be tumours, which begin with cellular proliferation around the blood vessels, to which a collagenous hypertrophy of the inter-vascular parts is immediately added; this would explain the regular fascicular appearance, as well as the predominance of the fibroma. At all events it is a mixed form of tumour, very closely related to fibroma.

Clinically, all fibro-sarcomata of the skin are firm, white to yellowish-white, well-defined tumours, which can often be shelled out from the skin. Of the primary multiple sarcomata, they correspond mainly to the first, but also to the second and fifth forms which I have described.

The partial transformation of the fusocellular sarcoma into myxomatous tissue is not to be regarded as a mixed form, in the same sense as the angio-fibro-sarcoma, but as a degeneration of the sarcoma, partly analogous to the change which takes place in fibromatous nævi, when they take the character of Fibromata mollusca. We are dealing, not with a combination with true myxoma, but with an œdematous, mucous softening of the already existing, fusocellular tissue. According to the seat of this, we may distinguish two groups: the *central* and the *peripherally* softening fusocellular sarcomata.

The former, which correspond to Funk's gummatoid sarcoma, show, after long existence, soft areas inside them, in which the collagenous inter-substance is converted into an œdematous mass, permeated by fine fibres, inside which the sarcoma cells partly perish, partly only lose their power of staining, and become rounded. When degeneration is advanced, the mass is quite unaffected by basic stains, and is permeated by spaces filled with fluid, consequently partially absorbed. Thus the sarcoma mass sinks in, and the tumour as a whole becomes umbilicated. We must distinguish from this central softening, which is accompanied by no vascular dilatation, and leads to general absorption, a peripheral one, which appears mainly in fusocellular sarcomata and fibro-sarcomata, when these are elastically projected from the rest of the skin. There then readily developes slight venous stasis, with œdema, at the periphery of the growth, and here and there a softening of the sarcomatous tissue, closely resembling true myxoma. The part of the tumour lying next the epidermis then shows a structure-like myxomatous tissue, wide vessels and capillaries, surrounded by large,

deeply stained, rounded cells, running almost naked through a rarefied connective tissue, in which are many spider and spindle-formed cells, with short processes, but still more widely distributed spherical cells, which have, some of them, distinctly developed from spindle cells, by swelling and rounding. The collagenous tissue consists partly of isolated fine fibres, partly of semi-solid inter-cellular substance. I had no opportunity of testing this for mucin; but the absence of refractility and metachromatic staining are against the presence of that substance. It rather seems as if there were only softening and partial absorption of the collagenous substance. A few leucocytes are always present in it, in addition to the cell forms mentioned, and here and there larger, multi-nucleated spindle cells; I have never found either mast cells or elastic tissue. This œdematous softening and liquefaction of the cells and inter-cellular substance sometimes extends a short distance into the healthy surroundings of the sarcoma, evidently under the influence of the venous stagnation at the periphery.

Central necrobiosis, although not altogether foreign to the fusocellular sarcoma, is so frequent an occurrence in the globocellular sarcoma that it is described there.

Round-celled Sarcoma.

When one passes from the study of the fusocellular sarcomata of the skin to that of the globocellular, he is inclined to recognise in the latter only a special variety of the former. The spindle cell is the normal cell form of the skin of adults, and there are certain parts in spindle-celled sarcomata, such as the vascular marginal zone, where we find rounded cellular areas, which have evidently developed from the spindles by amitotic division. But this view will not hold. The globocellular sarcomata (at least of the skin) are completely independent growths; they have their own laws of growth, different to and independent of the fusocellular sarcomata.

The fundamental difference is recognised at the first glance, in a well-stained section; the round-celled sarcomata contain numerous mitoses, which are practically never found in the spindle-celled form: indeed, I believe, from my present experience, that this is the main difference. The number of mitoses in the globocellular tumours is so great that we do not need to consider any other method of division, such as that described of the spindle-celled sarcomata.

Equally important does the difference in the method of development of the cells appear, as we can study them at the border of the sarcoma. Of nine round-celled sarcomata of the skin before me, this marginal zone is present in five cases, but is only available in

four, since one preparation, hardened in Flemming's solution, is not sufficiently clear as to the nature of the cells. In these four cases the sarcomatous degeneration begins in the healthy tissue with a swelling of the spindle cells, which may assume the same grotesque forms as in the neighbourhood of hard chancres. But the cells soon withdraw their processes, become round or cubical, while they secrete more deeply staining protoplasm, and thus partly form true plasma cells. From them, nearer the tumour margin proper, the true sarcoma cells develope, by breaking down of the protoplasm and loss of their staining capacity. This general occurrence of plasma cells, as a stage in the formation of sarcoma cells, is only found in the round-celled sarcomata, not in the spindle-celled, though, even in the latter, in the cases with vascular dilatation at the marginal zone, a few plasma cells may, as noted above, be observed. But there, their appearance is only an inconstant, unimportant, and much restricted phenomenon; here, *the plasma cell is the regular forerunner of the whole new formation;* it always remains cubical or round, without reverting to the spindle-celled type.

In this, the round-celled sarcomata rather approach the infective granulomata than the spindle-celled sarcomata, and they only have to be distinguished from the granulomata. The round-celled sarcomata of the skin may be divided into two distinct groups, according to difference in their whole architecture. Of my nine cases, seven belong to the group of the *diffuse*, two to that of the *figured* round-celled sarcomata.

I regard those sarcomata as *diffuse*, when from the margin of the tumour, the cellular masses—according as the resting collagenous tissue is more flat or cord-like—appear in uniform areas, as if formed of regular paving stones. In the *figured* round-celled sarcomata there is a certain contrast between the periphery and the centre of the cellular area, the deeply-stained elements of the periphery enclosing rounded, faintly stained collections of cells in the centre, and thus producing appearances, which at first sight recall tubercular and syphilitic affections of the skin.

The *diffuse round-celled sarcomata* are the true medullary, soft, rapidly growing, often hæmorrhagic and necrotic spongy tumours of the skin, which correspond especially to my third and fourth types of primary sarcoma, and appear as metastases on the skin in general sarcomatosis. Of the primary sarcomata, the subcutaneous tumours of Perrin's type also belong to this class. From them we may, as in the spindle-celled sarcomata, separate a group, which, by the greater amount of collagenous tissue which it contains, has a peculiar appearance on section, though the expression "fascicular" is not applicable. The collagenous

tissue disappears much more rapidly and completely under the influence of the growing round cells than under that of the spindle cells. Consequently, the tendency of this sarcoma to form mixed tumours, of the type of fibro-sarcomata, is much less than that of the fusocellular; a gradation from pure globocellular sarcoma to fibro-sarcoma does not exist. Most diffuse round-celled sarcomata of the skin reduce the collagenous substance to a fine fibrillary frame-work. Where, in exceptional cases, a new formation of collagenous tissue takes place, it does not grow regularly between the round cells; it surrounds, by more or less thick cords, areas of round cells, which endeavour to assume a spherical form, inside the ensnaring connecting substance. Inside these areas, the connecting substance disappears still more, and we have, as a whole, an alveolar or follicular structure of the new growth, in which purely cellular areas, which readily fall out of the sections, are enclosed and permeated by finer and coarser connective tissue trabeculæ. Thus the cut surface of this sarcoma has some resemblance to a bisected lymph gland, but not the same general arrangement, and the collagenous net which remains after brushing out the section suffices to clear up the diagnosis of its structure. For these alveolar round-celled sarcomata of the skin contain no leucocytes, but, like all sarcomata, a young growth of connective tissue cells. We describe them first of the round-celled sarcomata, because the genesis of the cell may best be studied here. Most of the firm connective substance early encloses a number of young cellular areas, and delays their development, so that, on almost every section of such round-celled fibro-sarcoma, we see all stages of the sarcoma cells.

The surroundings of the nodule look almost exactly like the neighbourhood of a tubercular or syphilitic plasmoma. All the spindle cells of the cutis are enormously enlarged, and form a perfect, communicating net of cells, while the blood vessels, hair follicles and coil glands are closely surrounded by much enlarged cells, among which there are always masses of plasma cells, and, in addition, further out, a few plasma and mast cells. The plasma cells are so closely collected in the lymph spaces around the tumour, that a reticular transitional zone is formed, in which pretty broad cords of plasma cells press asunder the firm, resisting collagenous bundles, an appearance which recalls certain parts of the syphilitic initial sclerosis. But this resemblance ceases immediately at the border of the tumour proper, for here the cellular cords suddenly swell up to large areas, and press the fibrillary connective tissue widely asunder; at the same time the character of the cells changes; from little characteristic plasma cells, they become the so-called round cells of the sarcoma.

As a fact, the cells are, at this place where they are enclosed by

swollen connected substance, no longer spherical, but, like the plasma cells from which they develope, angular, almost cubical. But when they are released from pressure they immediately assume a round form. Ordinary nuclear staining does not make this sufficiently clear. If one wishes to understand the nature of the sarcoma cells, he must use some good protoplasm stain, which hardly stains the nucleus. *Then he will see at once wherein the sarcoma cells differ from the plasma cells and the small cells of the infective granulomata.* It looks as if we had before us a collection of pale spherical nuclei, separated, like paving stones, by fine, deeply stained granular zones. But we soon see that the granules indicate the small protoplasmic body of the cell, and that it, in distinction to the round nucleus, is almost cubical. These deeply staining granules form what is left to the sarcoma cell of the deeply staining protoplasm of the plasma cell, and we find, as we advance from the border to the centre of the area, all stages of transition. Since the granules do not occupy all sides of the bodies of the plasma cells, but are irregularly scattered, these assume, with this stain, a peculiar atrophic appearance, characteristically distinguishing them from the small daughter plasma cells of the granulomata, with their very small but regular, deeply-stained protoplasmic rims.

An important characteristic of the sarcomatous round cells is the striking regularity in the size of the cell body, and still more of the nuclei, and the slight staining capacity of the latter, which, like all sarcoma nuclei, contain much nuclear juice and, in general, little chromatin. This relative deficiency in chromatin is in marked contrast to the many mitoses and the power of rapid proliferation of the sarcoma.

While the individual cells thus alter inside the large cellular areas, the original plasmomatic character, even in the centre of the nodules, is everywhere preserved, where the cells are enclosed by firm fibrillary tissue. Here they are still cubical, and appear on sections, as deeply stained, elongated, quadrilateral masses of protoplasm, with round clear nuclei, lying in the spaces between the collagenous bundles, often as regularly behind one another as the joints of a fungus in a hair. Evidently the stainable protoplasm is here preserved by the dryness of the tissue. This also contributes to the preservation of the elastic tissue in the collagenous septa of the tumour — as in the fusocellular sarcoma, — while, inside the cellular areas, the "alveoli," the elastin has of course altogether disappeared.

In opposition to these alveolar or round-celled fibro-sarcomata of the skin which evidently represent the rarer form, in the ordinary homogeneous round-celled sarcomata, the regular size of the cells

is much more evident, and gives a characteristic uniformity to the tumour. From the connective tissue margin to the hypoderm, all the connective tissue is gradually replaced by round or cubical, faintly staining cells, with round, little stained nuclei. The collagenous substance disappears, all but a few remains of septa, which divide the uniform cellular mass into irregular areas. Inside these, it is reduced to thin threads, which usually enclose series of cells, but sometimes individual cells. Inside this cell mass, which contains little collagen and no elastin, the blood vessels run stretched and almost naked; most of them are surrounded by pigment. Neither mast cells nor plasma cells are found in the interior of these nodules. But at the periphery, as in the round-celled fibro-sarcoma, we find a few plasma cells. These do not form large collections, nor do they form an enclosed shell around the tumour; we can only recognise small groups of these cells, by their reaction, at the margin of the healthy tissue, and thus learn that the genesis of the sarcoma cells, here, is the same as that described in fibro-sarcoma. In addition, there are also found numerous mitoses, which render an amitotic division of the cell masses improbable.

The less the plasmomatic character in these homogeneous nodules, the greater is their resemblance to Mycosis fungoides, and since the distinctions between these two utterly different growths are said by many (Funk) to be, even clinically, not sufficiently sharp, it is here our duty to define the histological differences as exactly as possible. Two points are to be borne in mind in establishing the by no means easy, histological differential diagnosis between round-celled sarcoma and Mycosis fungoides. Firstly, the appearances characteristic of the latter dermatosis are not the same at all periods, but they are always to be found in the later stages, and occasionally retrogressive. It is only in the fully-formed nodules that a confusion is possible; for the non-nodular commencement of Mycosis fungoides shows nothing sarcomatous. We select then, not the very youngest, recent nodules. Secondly, it is advisable to use a good protoplasm stain, for the differences are mainly apparent in the fate of the protoplasm.

A difference, recognisable even with the naked eye on the sections, and agreeing with the clinical one, lies in the superficial flat extension of the nodules of Mycosis fungoides, the skin being always affected from the papillary body outwards, the under part of the cutis and the hypoderm usually remaining free, while the surface epithelium shows by primary growth that it also is severely affected; this is in sarcoma only exceptionally the case; a true, flat and purely superficial extension does not there occur. This distribution, in most cases,

immediately establishes the correct diagnosis. But even on a purely cellular portion of the tumour, this is possible, if we pay attention to the following.

Diffuse round-celled sarcoma is distinguished by the uniformity of its cells, Mycosis fungoides by their polymorphism. In the latter, we find in every field a mixture of round cells, of all sizes, with all sorts of transitions to the spindle cells, which are preserved between them. The cell bodies are sometimes well defined, sometimes not, breaking up; they contain sometimes little, sometimes no chromophilic substance, but it is always in larger and more numerous granules than in the sarcoma cells, and—what appears to me most important—much more irregular. The nuclei are partly round and pale, like those of sarcoma cells, but some of them are deeply stained and have all possible elongated, distended, angular forms. Their numbers in the cells are very irregular, there may be one, two, three, or more, and in the same cell they take different amounts of stain. The only point in common, is the abundant presence of mitosis.

After the polymorphism of the cells, comes the greater succulence of Mycosis fungoides, which is clinically evident by the softness and compressibility. This is indicated, histologically, in the abundant presence of large and small lymph spaces and large lymph vessels. This point alone would serve for differentiation. But we note further, that in old and partly retrograde mycosis nodules, the lymph spaces contain, and are partly filled with, chromophilic nuclear fragments. Finally, I might mention the abundant presence of mast cells inside the mycosis nodule, as another difference; inside the sarcoma nodule these always rapidly perish.

In conclusion, we have to recall the luxuriance of saprogenic flora in ulcerated mycosis nodules, which is almost typical of them, and much greater than in ulcerated sarcomata.

Thus the often noted resemblance of Mycosis fungoides with diffuse round-celled sarcoma does not appear so great that confusion should occur, and the separation of these sarcomata from the infective granulomata is still simpler. Only the round-celled fibro-sarcomata might present difficulties, on account of the number of plasma cells they contain, did not the further transformation of these cells into the uniform sarcoma cells at once dissipate all doubt. In the other round-celled sarcomata, the number of plasma cells is so small, that a comparison with the infective granulomata is unnecessary.

But in this connection, in describing the second form of round-celled sarcoma, the *figured round-celled sarcoma*, the case is different. These tumours have absolutely no resemblance to Mycosis fungoides, but they have very close analogies to the infective granulomata,

especially Tuberculosis and Syphilis. Here, if one is anxious, he may speak of a transition between sarcoma and infective granuloma.

This group is characterised, clinically, only by solitary, slowly growing, smaller nodules, of a brownish or bluish colour, localised on the ends of the extremities, and the face, which recur locally, but do not give rise to metastases. The periphery of these nodules resembles that of the diffuse round-celled sarcoma, especially the alveolar. We find a broad zone of hypertrophic spindle cells, with groups of true plasma cells, and with individual plasma cells scattered between round sarcoma cells of the ordinary nature, and permeated by very much distended vessels. From the margin of the tumour, streaks of this sarcoma tissue extend into the centre of the nodule, and also show a few plasma cells. These cords, which are rather like diffuse sarcoma tissue, enclose *peculiar central areas* of quite different structure, which are characteristic of this "figured" form of sarcoma. With a protoplasm stain, they are very evident as clear, confluent circles, with polycyclical borders, which are surrounded on all sides by the deeply-stained, young sarcoma tissue; they look exactly like the pale centres in the tubercular plasmoma. And indeed, we are dealing here, as there, with distended, frequently multi-nuclear cells, homogenised through the loss of all basophilic stainable substance, which compress the neighbouring cells, which are also clear, but not distended in the same way, into half moons and sickles. The latter surround the former, and thus produce the polycyclical, figured appearance of the whole.

To complete the analogy with the infective granulomata, we find giant cells also in these sarcomata, mostly at the margin between the paled centre and the adjacent, ordinary sarcoma tissue. This is a very noteworthy observation. For the presence of giant cells in cutaneous sarcomata in general, is no such self-evident factor as might perhaps appear from analogy with other sarcomata, especially of the bones. The spindle-celled sarcomata only very rarely show the formation of large multi-nuclear spider cells and small chorio-plaques. In the round-celled sarcomata, the tendency to rapid and complete cellular division arrests, at the commencement, any tendency to the formation of giant cells. Only where they undergo myxomatous degeneration, with rounding of the other cells, do large multi-nuclear cells appear. In those cutaneous sarcomata which develope from sarcomata of bone beneath, giant cells may of course be abundantly present. But a proper giant-celled sarcoma of the skin, *i.e.*, one in which the giant cells form a necessary stage of development of the tumour cells, which might be placed along with the spindle- and round-celled sarcoma, as a type, is certainly very rare. I have only seen this once, and will here describe it.

Giant-celled Sarcoma.

This was a small, bluish-red, angioma-like tumour of the face, which Dr Gutsch kindly gave me. The whole cutis was transformed into a tumour mass, with numerous cells and very little inter-cellular substance, over which the epidermis was here and there thinned, and in one place ulcerated. At the base there was a little unaltered collagenous tissue, and here it was evident that the tumour cells developed from spindle cells, which, by taking up protoplasm, at first around the nucleus, enlarged, and then assumed all possible forms and dimensions. The cells are so multiform, that it is hardly possible to describe them ; in their cubical, concave forms, often connected by bridges, they recalled most, the epithelia of alveolar cancers. Almost all of them contained several nuclei, and the larger ones also contained vacuoles, with nuclear contents. They passed very gradually into the giant cells, with which every section swarmed. On an area one millimetre square, there were about fifty or sixty, smaller or larger, very granular giant cells, of the most varied form, and usually possessed of broad processes, by which they were partly united. They all contained, in their methyl-blue stained bodies, a considerable number of irregularly distributed granules, but also whole enclosed cells, especially hyalin degenerated cells, with well-preserved nuclei ; and in addition there were many vacuoles, from which such cellular enclosures appeared to have fallen out. They apparently increase by taking up such complete cells, which they surround, and which are found sticking half into their borders, and also inside them, showing distinct round contours and a diminished protoplasm stain. The slight frame-work consisted of numerous wide vessels of capillary character, and very fine collagenous fibres, which were partially mucoid and no longer took the ordinary stain of collagen. The perithelia of the vessels were much enlarged, but not the endothelia, and the giant cells certainly did not develope from vascular endothelium. Elastin and mast cells were completely absent.

The occasionally colossal cells of this tumour were certainly not true giant cells, if we regard the tubercular giant cells as typical. That requires a tendency of the nuclei towards one pole, or the formation of a peripheral wreath, a certain regular form and size of the nuclei, and a spongy and cloudy character of the protoplasm, with loss of its basophilic character. Here, and in the sporadic giant cells of other sarcomata, we are dealing with large chorio-plaques, which in this case certainly determine the character of the whole growth.

But true giant cells are found in those sarcomata of the skin, which I have described as " figured." Their occurrence is constant in

the three sarcomata (two from the face, one from the finger) from which I took the description, but their numbers vary very much. The number of nuclei varies considerably (6-100 and more), the very large ones can scarcely be distinguished from tubercular giant cells. Their main seat is the margin towards the central pale tissue, which in some places is almost composed of giant cells, and separated from the rest of the sarcoma tissue.

This last character further divides the giant cells under consideration, from those scattered in all parts of the plasmoma, and especially from those frequently occurring in the central parts of the infective granulomata. But these are clearly distinguished from the figured sarcomata if, in every case, we bear in mind the genesis of the pale cells; here they develope from typical sarcoma cells, with fragments of stainable basophilic substance in the small cell body; in the infective granulomata, directly from plasma cells or their daughter cells, which possess, though only little, deeply-staining protoplasm, and whose nuclei show more chromophilic substance. A confusion of this sarcoma with the granulomata should not occur, but it cannot be denied that the two forms have their resemblances, though the figured sarcomata of the skin are the only ones which require differential diagnosis from the granulomata.

We can shortly explain the granulomatous look of these sarcomata, by the fact that in them the ultimate product is, not the sarcoma cell, but a swollen, homogenised cell, or a giant cell, just as in the infective granulomata. On this may depend the stability and relative benignancy of these sarcomata. We have therefore to distinguish in them two stages: the purely sarcomatous and the figurated; in the latter, the younger constituents are at the periphery and in some of the processes penetrating the nodule, while further development takes place in the centre. As indications of the proliferation, we have at the periphery —as in other round-celled sarcomata—numerous mitoses, and in the centre, multi-nuclear and giant cells, whose nuclei have multiplied amitotically. Further degenerations, analogous to the caseation of the infective granulomata, I have found just indicated in the figured sarcomata. But I do not doubt, that if the tumour were left long to itself, degeneration with drying up would result, just as in the granulomata. For, the necessary conditions, the disappearance of the blood vessels and lymphatics, are here also present, and the dryness of the central tissue is marked, while at the periphery—as already noted—there is an unusual dilatation of the blood and lymph vessels; here again the periphery and the centre of the figured sarcoma are as different as possible. But I have not observed, in the figured sarcomata, the ordinary degenerations of the diffuse round-celled sarcomata, on

which I must now say a few words. They are mainly: *mucous* (myxomatous) *softening*, *hæmorrhagic pigmentation*, and *necrosis*.

Mucous softening, which represents a great proportion of the centrally softening, large nodular forms of the skin (Neumann and Funk) and of the hypoderm (Perrin), affects the round-celled like the spindle-celled sarcomata, usually in small segments, corresponding to one vascular territory. The round-celled fibro-sarcomata most resemble the softened fusocellular, for here also the ground substance is all along firm. The softening is indicated in these cases, in a coarse-pored running together of the ground substance, and dilatation of the lymph spaces, which are filled with a mucous, homogeneous or granular, pale liquid substance. But a number of stronger collagenous trabeculæ persist in the affected area, and many of the cells adhering to them are protected from solution. These enlarge, and, being freed from the pressure of the firm tissue, partly swell up and occasionally show amitotic division of the nuclei. The impression one gets is that of a simple œdema, with swelling and partial absorption of the cells and inter-cellular substance.

Rather different appearances are induced on the pure round-celled sarcomata, the degeneration of the affected areas being more regular and severe. All the collagenous tissue, as well as the cell protoplasm, is converted into a finely fibrillated, brawny mass, so that, for a time, the nuclei lie naked in the softened ground substance. Later on, the nuclei also disappear, and the whole area, sharply marked off from the rest of the sarcoma tissue, is converted into a regular, a-cellular, slimy tissue, which does not stain with basic colours. By the confluence of such elementary areas, large stretches of the sarcoma may soften, and we usually see in them wide vessels, almost free. On absorption of the fluid inter-cellular substance, the nodules sink in (spontaneous regression of the sarcoma nodule), but with the addition of external ulceration, they undergo rapid purulent breaking down.

A very frequent change in all round-celled sarcomata of the skin, is an ever deepening pigmentation, which is to be ascribed to the hæmorrhages, and the deposit of golden-yellow blood pigment. The change is evident, even macroscopically, in the darker colour of the nodules, and on the cut surface, in yellow and brown streaks, which alternate with lighter parts. Where fresh bloody suffusions are present, the colour of the spots is bluish-brown to black. The hæmorrhages, also, usually correspond to a small vascular territory, but since the bleeding often extends for some distance along the vessels in the accompanying connective tissue, the hæmorrhagic territories always have long, streaky processes. The fresh hæmorrhages show the blood corpuscles closely packed, surrounding and pressing asunder

all the sarcoma cells. Older hæmorrhagic areas contain, instead, golden-yellow pigment, in innumerable granules of varied size, partly in, partly outside the sarcoma cells and the cells of the interstitial tissue. Here and there all the cells are, without exception, converted into coarse, pigmented lumps, in which, with great difficulty, one can recognise only one nucleus. The colour of the pigment varies from light golden-yellow to brownish-yellow, and granules of different coloured pigment may lie in the same cell. But I have never seen the blackish-brown colour of melanotic tumours.

A connection between the partial necrosis of the round-celled sarcoma and the hæmorrhages is not recognisable, but the latter at least frequently favour the development of the former. We often find the coagulated necrotic parts permeated by ecchymoses, and pressed asunder, and further, we find blood pigment free in the necrotic areas or at their borders, in the still unchanged sarcoma tissue. It is therefore not unlikely, that a bloody suffusion in the so loose cellular tissue might arrest the circulation, but every necrosis of the round-celled sarcoma cannot be attributed to this, for often there is no sign of bleeding. Then the necrotic parts are usually more sharply margined than the hæmorrhages present in the same preparations. The sarcoma cells lose their nuclei, and are converted into unstainable fragments, along a definite line. This change then extends equally to a larger area of the sarcoma, and passes at the other side, equally sharply, into ordinary sarcomatous tissue. These necrotic areas have the most varied forms, but their borders are usually convex.

We will most correctly estimate all these degenerations, which are all distinguished by their strict limitation to small segments of the sarcoma tissue, and their sharp margins, from the same point of primary vascular changes; the œdema and the circumscribed softening, the hæmorrhages and the necroses. Although the frequent statement, that the vascular cells form the basis of the sarcoma tissue in general, is not tenable for the cutaneous sarcomata, it must not be denied that in the sarcomatous processes, the otherwise so well preserved cutaneous vessels are often robbed of their outer protecting coverings. Lesions of any kind, partly external, partly internal, combined with the growth of the tumour, will therefore induce tears, bends, stases, hæmorrhages and thromboses with their results, more easily than elsewhere.

Other degenerations of the sarcoma tissue are of course not excluded; hyalin degeneration, which I have often found in the fusocellular form, appears to be rarer in the round-celled sarcoma. The fatty degeneration, so often referred to and stated to be generally present,

requires fresh investigation with the assistance of modern technique; in the little material which I have treated with osmic acid, I can discover nothing of fatty degeneration of the round cells.

I say nothing of metastatic "melanotic sarcoma" of the hypoderm, for the two cases given me as such, proved to be metastatic carcinomata, and one of them had demonstrably developed from a primary pigmented nævo-carcinoma. The future must teach us whether this group should be maintained.

Possibly the pigmented malignant tumours may be divided, more simply than we previously believed, into hæmorrhagic pigmented sarcomata and melanotic pigmented carcinomata.

With this simple solution, the existence of Virchow's Sarcoma carcinomatosum would come to a peaceful end; it is a type, found mainly in melanomata of the eye, which partly show the alveolar form of carcinoma, partly that of spindle-celled sarcoma. For the benefit of future investigators, it may be noted that the large cellular nævo-carcinomata are partly composed of the most perfect epithelial spindles. (See Nævo-carcinoma.)

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(B). Benign New Formations.

The knowledge of the germinal layers has led to a much better comprehension of the benign tumours of the skin, and a strict classification of them, in this sense, was first introduced by Auspitz. This he could the more easily do, as he was the first to emancipate himself from the incorrect views on papilloma of the skin, and definitely to place the group of so-called papillomata, which hung between epidermic and cutaneous tumours, with the epidermic tumours, as Acanthomata.

Since then, the position of the benign tumours of the skin is much simpler.

But it cannot be denied, that, with our present views on tumour formation, there is another and more important aspect from which to divide the tumours, than that of the two germinal layers, which constitute the skin. I mean that fundamental difference in the formation of the tumours, which depends on the fact, that certain of them are formed from the proliferating tissue itself, while others only represent tumour-like collections of inert, even dead, or at least not independently growing tissue. Among the latter, the cysts, for example, have always been reckoned, and since they deviate so from the character of proper tumours, they do not seem altogether at home in that group. But the *stagnation of no longer proliferating tissue elements*, which is the principle of growth present in cysts, is by no means limited to these structures. An entire, very important class of epidermic tumours, the keratomata, also depends upon it, though here the stagnation does not take place in enclosed spaces, but on the surface of the skin. For we now know definitely, that under no circumstances can the horny cells proliferate independently, nor do they undergo, without an increase in numbers, a simple hypertrophy of the cells, and thus lead to the development of a tumour. We have rather to do in all keratomata, however different they may appear, with a stagnation of horny cells at certain places, and the size of these tumours (*e.g.*, in cutaneous horns) is often in marked contrast to the small power of production of the cells, exactly as in many cysts.

If we pursue this line further, we find a large number of tumours with the same stagnatory mode of growth, and we usually find that they have, more or less unknown to the authors, been therefore treated somewhat differently from the true proliferative new formations. We know very well, for example, from the pigment of the skin—it is one of the few things regarding pigment which is not doubtful and contentious—that there are no independent pigment bodies, which multiply independently, and thus induce the well-known pigmented tumours of the skin, but that these all depend on a gradual stagnation of pigment, which may have come from the blood or elsewhere. There is therefore a special group of pigmented tumours among the true new formations; but were we to find it necessary to form a whole *class of stagnatory tumours*, the excessive pigmentations of the skin would be included in it. At least they belong neither to the connective tissue, nor to the epithelial tumours.

The same holds of a tumour-like collection of mast cells. For, since we know that they develope, by a special progressive change, from ordinary connective tissue cells, and do not usually further

increase by division, so that their numbers depend only on the ever-increasing collection of transformed spindle cells, they also belong—*i.e.*, as yet only Urticaria pigmentosa—to the stagnatory tumours.

Much confusion and many just doubts have ever prevailed in the region of the angiectases. As certainly as there are true angiomata, which develope from continuous new formation of blood vessels, so certainly is the union with them of a series of equally certain angiectases, a mistake which can only be excused, because we did not possess a recognised class of stagnatory tumours. It was therefore always tempting to give to the angiectases, so to speak, "the freedom" of the true tumours, laying special stress on the fact, that even in them tissue proliferation was not altogether absent. What was gained by pressure on the inner walls of the vessels, and the stagnation, was said to become a definite part of the angiectatic growth by simultaneous and subsequent endothelial growth. But this subsequent endothelial proliferation gives the angiectases no more the position of true, growing tumours, than the necessary new formation of prickle cells gives the keratomata. That depends on whether the actual tumour-forming factor is formed by independently proliferating, or merely retained masses of tissue. According to this definition, all angiectases belong to the stagnatory tumours.

It requires no long explanation, to show that all lymphangiectases should also come into this class, and be separated from the true tumours. But that the lymphangiomata, in contrast to the angiomata, also belong to the lymphangiectases, I shall, I think, be able to make clear. The honest investigator who has to work through this, no doubt very interesting, but most obscure and intricate region, shudders at the very recollection. I can hardly believe that, by looking at it from this other side, I have fully cleared up this question, but I am convinced that a final recognition of the lymphangiomata, as stagnatory tumours quite different from the angiomata, will spare much superfluous search after non-existent tumour-forming elements.

It will appear strange to many pathologists that I place even the lipomata * of the skin under the stagnatory tumours. Strictly speaking, this is correct. For the fat cells do not proliferate as such; the fat in them prevents that, and they must first lose it, before they can proliferate. Lipomata therefore develope, exactly like normal fatty tissue, by the successive deposit of fat in an ever-increasing number of connective tissue cells; we have then a retained collection of fat. Long ago, before I reached this train of ideas, I attributed the lipomata, like the development of the fat in the skin generally, to a stagnation of fat-containing lymph.

* Xanthoma I rank provisionally under the stagnatory tumours, for reasons there given.

It may perhaps be objected, that this goes beyond the proper region of the stagnatory tumours, and that we would have to include many, especially the fibrous new formations of the skin, in this class of tumours. As a fact, the collagenous fibres do not proliferate; they do not increase independently, yet they form distinct tumours. But there is a noteworthy difference. Some of the fibromatous tumours are more than half cellular in nature, and therefore belong, without question, to the true proliferating new formations. Others, especially Keloid, consist mainly of collagen, and increase, from a certain period, without new formation of cells. But here there is real activity, and not simple stagnation, for the collagenous substance undergoes progressive changes, swelling up, and thus mainly inducing the tumour formation. The fat cell is not capable of this; it can only hold so much, and then bursts and discharges its oily contents.

We see then that the class of stagnatory tumours is by no means small, indeed it is more comprehensive than that of the true proliferating tumours. This experience alone, but still more the new arrangement of many tumours in particular, and the closer relations into which many, previously separated, come, should certainly give rise to consideration, and lead new workers into this region, which has previously been rather ignored in dermatology.

A special discussion is due to the classification of the congenital, benign tumours of the skin, the Nævi. Were it not the plan of this whole work to treat congenital malformations apart from acquired changes, I could hardly have resisted the attempt to class Nævi with the benign tumours. For in many points the definition of these malformations of the skin is excessively difficult. It is not because these congenital tumours cannot be recognised as nævi, that it is easier on the skin than anywhere else. But herein lies the difficulty, that in the skin we note, better than anywhere else, that there are many more congenital tumours than are noted at birth. Especially in the Angiomata, Myomata, Neuro-fibromata, glandular tumours of the skin, in certain forms of Elephantiasis, &c., the distinction between congenital and non-congenital is very difficult, is often artificial, and leads to unavoidable repetition.

On the other hand, there is here, in the attempt at thorough separation, a stimulus to the further investigation of the nature of these tumours, and to the use of all histological means in order to bring light into this dark region. Thus, for example, only to mention one case, I was able, by the recognition of micro-organisms in the centre, to determine the acquired nature of a sebaceous cyst, which at first looked like an Atheroma.

(α). Tumours Proper.

1. *Tumours of the epidermis.*

The benign tumours of the epidermis and the epidermic appendages are now more easily and clearly distinguished from those of the cutis than ten or twenty years ago, when the class of mixed tumours, the so-called papillomata, though scientifically attacked on many sides, still maintained their position. Virchow in vain advised the abandonment of the word papilloma, which involved the assumption of an independent growth of the papillæ of the cutis into an organised form of tumour, analogous to Angioma and Neuroma. In vain Auspitz contested this tradition of independent papillary growth, with all the logical acuity and proofs available to him; he was only able to convince independent thinking experts. For the profession in general, the definition of the "papilloma" was unimpeachable, and indeed was used with great satisfaction in practice. No one enquired after the justification of the word, papilloma; the simple fact that a number of scientific articles and chapters in text-books were so headed, sufficed to sanction the further use of the term, and, according to his taste, each one understood, under this convenient term, the most varied growths; warts, condylomata, cutaneous horns, nævi, and in general all benign tumours of papillary form.

I have often taken the opportunity of fulminating against this superficial and unscientific term. But I do not flatter myself, although now—at least in Germany—the day of the papilloma is nearly over, that my arguments are any more convincing than those which Auspitz brought forward. As is always the case in deeply-rooted prejudices, help came from quite another quarter. Cohnheim had gradually been able to convince all pathologists of the infectiousness of tuberculosis, but that made no impression on the medical world—that was reserved for the discovery of bacillus. And it would have been possible for all pathological anatomists and investigating dermatologists to have understood the unsuitability of the term papilloma, without the term being generally abandoned. The discovery of mitosis, as a ready and certain indication of the region where proliferation was going on, was the first thing to shatter for ever the faith in the papillary growth, and it is now fast disappearing. In England, America and France, the expression is certainly still in use by experts, but even there its days are numbered, and it is no longer possible for a leading histological text-book to maintain the term, papilloma.

Much of the tenacity, with which it was held, may have been due to the fact, that a short and descriptive, in a word, a handy expression

was long awanting for those epidermic tumours which pass as papillomata. The word epithelioma is not altogether unsuitable, although rather too comprehensive, for it also includes the keratomata; but it cannot be used, on account of the ominous sound which it acquired during the long strife on the histological nature of cancer. Auspitz again came to the rescue. By introducing the word *Acanthoma* (growth of the prickle layer), he has freed us, at one blow, from the indefinite "epithelioma" and the useless and incorrect "papilloma."

All the tumours, which were previously regarded as papillomata, belong to the acanthomata, for on the skin the papillary form is always combined with a growth of the prickle layer—one may indicate with the adjective papillary, every granular surface, *e.g.*, that of ordinary granulations, though with no special reason. On the other hand, the acanthomata comprise many epidermic tumours of non-papillary form. In the initial stage, most of the later exquisitely papillary growths, have usually a flat or button form. But even if, as rarely occurs, the papillæ in an individual case exactly correspond to those present on the affected part of the skin, and these have assumed larger dimensions, we never find active papillary budding. Usually the new papillæ by no means correspond to the old; they are generally less numerous, even if the papillary acanthoma is of considerable size. Finally, in the few cases where, as a result of the proliferation, the number of papillæ shows an increase, the growth which determines their form, as is now shown by the mitosis and previously by their whole structure, lies solely in the epithelium.

It might appear necessary to separate papillary and non-papillary growths. But this division is, on the one hand superfluous, and on the other unsuitable. For, however striking the papillary formation may appear, clinically, in individual cases, it is in no case the main character of the tumour in question, and is not present at every period of development. Usually the complicated papillary arrangement is a sign of the age of the tumour, and therefore, if one will, of its higher development. How the papillary formation developes must be discussed in the different acanthomata. Where similar conditions are found in other epithelial tumours, especially carcinomata, papillary formation is also evident.

In addition to the acanthomata, there belong to the true proliferating epidermic tumours, only the glandular hypertrophies and adenomata, for we have placed the keratomata, which are usually included in this group, under the stagnatory tumours of the epidermis. Epithelioma contagiosum belongs to the first group of acanthomata of the surface epithelium, and not to the follicular tumours, as some dermatologists still believe. And the acanthomata, proceeding from the

follicles and coils, are considered in the latter group, from their near relation to the hypertrophies and adenomata of these organs.

(a). *Acanthoma.*

Verruca vulgaris.

An acquired acanthoma, of infectious nature, appearing in areas, to which hyperkeratosis is immediately added. Ordinary warts occur on the hands, wrists, around the nails, more rarely on the face, almost never on the covered parts of the body, in children or young people as well as in older ones, whose occupation necessitates washing and cooking ; they are single or in groups, and sometimes in enormous numbers. They reach semi-spherically over the surface of the skin, are hard, $\frac{1}{2}$-4 millimetres in diameter, rarely more, but they may run together into polycyclical patches. Old warts show, by the throwing off of their upper horny layer, their papillary formation, but never a transition into cutaneous horns. Their frequent rapid spread among children and servants, and their equally sudden disappearance, their growth on fine cracks and fissures of the hands, or in the form of streaks on fissures of the epidermis around older warts, make their infectious nature very probable. Kühnemann has recognised a bacillus in the prickle layer of common warts. The following structures, which are frequently called warts, do *not* come under the definition of *Verruca vulgaris:* 1. Condyloma (condyloma acuminatum) also known as the acuminate wart. 2. Fibro-keratoma of the eyelids and of the neck of old people (also called Verruca filiformis). 3. Verruca dorsi manus (also called Verruca plana). 4. Verruca seborrhoica (also called Verruca senilis).

Histologically, we distinguish three distinct stages in every individual wart, that of commencement, that of acme, and that of regression. The first stage is characterised by a patchy thickening of the prickle and horny layers. By the simultaneous acanthosis and hyperkeratosis, the papillæ on the affected area of skin, with few exceptions, are depressed, and the papillary body, as a whole, is passively stretched and flattened. The few, invariably vascular papillæ, which resist the epithelial growth, are thinned and elongated. The granular layer is regularly thickened, as is the horny layer, and many but not all the nuclei are preserved. Thus the commencements (about $\frac{1}{2}$ millimetre in diameter) in the neighbourhood of older warts, appear as pure cornified acanthomata, without any inflammatory appearances in the cutis.

But this alters as the warts enlarge. When they have reached a diameter of two millimetres or more, new formed epithelial taps and ridges commence to grow into the cutis, which now shows reaction in the form of a dilatation of the papillary vessels ; a quite superficial hyperæmia, which does not extend beyond the sub-papillary vascular net. The perithelia of the vessels, also, are somewhat more numerous and larger than normal. The reaction of the cutis is limited to these

slight changes, which must be regarded as a very slight inflammation. It is worthy of note—and indicative of the benignity, the superficial character of the affection—that the cutis opposes considerable resistance to the penetration of the epithelial ridges. At their ends these are never broad, but pointed and bent towards the centre of the wart, so that, on perpendicular sections which are not exactly through the central parts of the wart, we have the appearances of an epithelial net instead of processes. Therefore the wart is never deeply rooted in the cutis, and may be easily and completely removed with a sharp spoon. From the bending of the external ridges towards the centre, the under border of the epithelial growth, as a whole, frequently takes a rounded goblet-form. The growth of the epithelium is soon arrested, and we have simply a slight dimpled depression of the cutis, from whose centre arises a common papillary trunk, which expands above, and is lost in a number of long thin papillæ. G. Simon had already recognised that the number of the papillæ in a wart was very much less than normal. He attributed this to their coalescence, which hardly agrees with the fact that the form of the papillæ is preserved. Simon did not know the mutability of the papillary surface. The diminished number of the papillæ is simply due to the fact, that the primary acanthosis at once flattens out a great number of the less resisting papillæ. With the advancing epithelial growth, which endeavours in vain to snare off new papillæ from the surface of the cutis, their numbers do not alter, only their form. They now acquire a broader fixed end, and where the peripheral ridges are passing inwards, the papillæ in connection with them also bend their fixed ends towards the centre, and there combine, as already noted, into a common papillary trunk. Now and again, small, secondary papillæ are furrowed out by very small epithelial buds. This point has rightly often been noted; it is in contrast to the relation of the germinal layers in condyloma. While in the latter the broader and more succulent papillæ always undergo secondary furrowing by the epithelium, all along their length, that either does not take place in the wart or, if it does, is limited to the widened lower end.

The less the prickle layer penetrates into the cutis, the more does it collect on the surface into a thick cushion, which is always regularly arranged around the persistent papillæ. The prickle cells at the cutis margin are small and closely packed, contain numerous mitoses, and swell up considerably in the upper layers, so that the cells retain their considerable size even in the granular layer, and occasionally in the horny layer. The inter-cellular lymph spaces, in which Kühnemann's bacilli may be recognised here and there, are wide, and may even be seen in the granular layer. This is always widened to ten layers and more, in the depressions between the papillæ; above the papillæ the

number of layers and the size of the kerato-hyalin granules notably diminish, but even the apices of the papillæ are in most cases covered with one layer of finely granular cells. But the papillæ, which have reached very high in the wart, and are almost always covered by small hæmorrhages, have their apices quite free from a kerato-hyalin mantle. According to Kühnemann, the elëidin varies in proportion to the kerato-hyalin. The horny layer at the height of development always contains nuclei. In the inter-papillary depressions, the nuclei are absent, but again appear at the sides and over the apices of the papillæ. No medullary substance is ever developed over the apices of the papillæ in warts—in marked contrast to cutaneous horn ; this is no doubt to be attributed to the softer and looser quality of the horny substance in the wart. The sweat pores, which of course always penetrate the warts at the position of the epithelial depressions, are surrounded by a normal horny column, and are more stretched than normal. They form a very steep spiral or a perfectly straight, narrow tube, with a somewhat dilated external opening. This abnormally straight course of the sweat pore is in favour of a harmonic advance of the duct and the surface epithelium ; normally, the latter is much slower than the former, and in corns and callosities—in direct contrast to warts—is still slower than normal.

Where lanugo hairs are found in warts, they show no changes, and do not participate in the growth of the surface epithelium, but are simply enclosed in it.

Leucocytes are only found occasionally in warts, and the papillary body beneath shows no trace of emigration.

The border of warts, at their acme, is steep, but the immediate surroundings are not completely normal ; a small area around shows, in a diminished degree, growth of the prickle layer, thickening of the horny layer, and dilatation of the papillary vessels.

In the third stage, the wart has passed the stage of maturity, and the new formation of prickle cells is arrested. We no longer find mitoses in the prickle layer. But since the cornification of the already formed epithelial cushion continues, the horny layer is constantly going deeper into the inter-papillary depressions. In the upper, older parts of the ever-increasing horny layer, there appear small tears and large fissures, and finally wedges of horny material break off from the inter-papillary parts, and display the papillary formation of the wart. The papillæ, clothed with their persistent horny sheaths, gape on all sides like expanded fingers, and by this altered position, and the tendency of their apices to turn outwards, draw attention to the centripetal constriction of their base at the bottom of the wart. So long as the wart grows, and is found at the height of its development,

there exists a tension of the connective tissue axes against the epithelial cement, which surrounds and holds them together; this tension is induced by the epithelial growth at the base, which cannot extend freely downwards or outwards, and therefore, from all sides, compresses the papillary body at the base of the wart.

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Condyloma.

The Condyloma is a *pure acanthoma, appearing isolated around the mucous openings and on moist and seborrhœic areas of skin, and tending to extend superficially.* The tumour, mainly known as "condyloma" (condyloma acuminatum), begins as a small button, which soon becomes lobulated, and by further furrowing assumes, in most cases, a cauliflower appearance. The colour is at first that of the tissue in which it grows, on the mucous membranes and their borders, red, on the skin, whitish-yellow; it afterwards depends on the degree of cornification. Waxy, yellow, transparent condylomata may be seen arising from the red corona of the penis. Those which develope on the head and in the naso-labial furrow, on a seborrhœic basis, are usually pretty hard, dry, and yellowish, and thus suggest ordinary warts (Verruca vulgaris), with which they must not be confused, for their formation is that of Condyloma. Clinically, Condyloma is distinguished from the wart by the fact, that preparatory changes of the matrix (suppuration, seborrhœa, eczema), and not simply tears in the horny layer, are necessary for the successful growth of the condyloma "germ," by the fact that they extend continuously in a serpiginous manner (contact folds), so far as the conditions of the soil are suitable, and that they show no remission and spontaneous arrest, but rather grow into very extensive tumours, which can only be arrested by artificial means.

Since condyloma undergoes no spontaneous regression, we can only distinguish, even histologically, two stages.

In the first there is, exactly as in the wart, a patchy thickening of the epithelium, under which the papillæ are depressed and flattened out. Then there appears at one place, a button-like projection of epithelium, which is macroscopically visible as a very fine point. The growing epithelial ridges, as in the wart, do not penetrate deeply, nor do they depress the papillary body at the base; they are rather elevated by the more and more swelling papillary body. The elevation over the surface is, at the commencement of condyloma, largely due to the swelling cutis, while later on, the epithelium is greatly in excess. But if the projection and the increase in size of these tumours is partly to be attributed to the connective tissue, the active formation is the function

of the epithelium alone. Here, as everywhere else, the cutis only has a passive influence on the definite form, owing to the presence of already existing points, different in their firmness and resistance. The simultaneous appearance of many projections gives the surface a finely granular aspect.

FIG 29.—Condyloma.

Stages (*a*, *b*, *c*, *d*) showing the development of a Condyloma.

In the second stage, the condyloma grows to the well-known cauliflower or finger-and-toe shape, or only forms simple button-shaped growths. During this period, there take place, in the epithelium as in the connective tissue, numerous changes, which are always making clearer the distinction between Condyloma and Verruca vulgaris. The epithelium proliferates very luxuriantly; we find mitosis, not only in the basal layer of the prickle cells, but, as in certain carcinomata, even in the fourth, fifth, or sixth epithelial row. The prickle cells are very much enlarged, just as in actively growing carcinomata. It is no rarity to find prickle cells four or even eight times the size of those of the neighbourhood. The lymph spaces between the prickle cells are greatly dilated, and the connecting bridges of the cells, which they

traverse, unusually well developed. These latter are penetrated in many places by spirals of fibrin (Herxheimer, Eddowes), often in astonishing amount and extension. Where the lymph spaces of the epithelium are very wide, the connecting prickles of the epithelium are sometimes drawn out to long bristles; and such may be seen to connect two epithelial cells at a distance, which, from the presence of other cells between them, are only seen to be connected by those bridges. Granular and thready fibrin is found in varying amount in the granular and horny layer, in the latter, closely packed between the cornified cells.

Everything points to an exceptionally luxuriant nutrition of the epithelia, and a growth of the prickle layer in all directions, from abnormally numerous points. The granular layer is as broad as in warts—an invariable sign of delayed cornification. But it is not succeeded, as in warts, by a much thickened horny layer. The cornification here, except for the delay, is normal; the horny layer is of the same thickness as on the surrounding skin, or only very moderately thickened. There is no hyperkeratosis,* no abnormal adherence of the horny cells, and thus, on the one hand, no retention of horny masses, and none of the horny cement, which in warts holds the papillæ together, and, on the other hand, no firm external shell, whose resistance forces the epithelial ridges downwards. While in the wart the cornified epithelium forms the main mass of the tumour, the uncornified here predominates. Thus the external form of the Condyloma is quite different. In order to understand this thoroughly, we have to study the simultaneous changes in the connective tissue trunk. This is very rich in blood and lymph, and penetrated by widely gaping vessels and lymph spaces. The ascending capillaries of the papillæ have sometimes the calibre of cutaneous veins, and reach to the free ends of the papillæ. In the wide lymph spaces, there are found extensive nets of fibrin, fibrinous lumps, and much granular fibrin; fine threads of fibrin sometimes penetrate the connective tissue, and extend into the fibrin spirals of the epithelium. The connective tissue contains an excess of spindle cells, often of very considerable size, as well as an abnormal number of leucocytes, which find their way into the epithelium. More severe local leucocytosis is only the result of some additional disturbances, such as caustics, or breaking down of the tissue. Mast cells are always found in the new-formed connective tissue in considerable numbers; they are large and multiform, but rather round in form than elongated. But they are particularly motile in Condyloma, for we can always find a number (as in certain carcinomata) which have wandered into the lymph spaces of the epithelium.

* One of the proofs of the absolute independence of acanthosis and hyperkeratosis.

Thus we grasp the somewhat complicated structure of Condyloma, as it gradually developes, and the striking difference from Verruca vulgaris. In both cases the papillæ are, only to a minimal extent, the direct derivatives of the papillæ of the mother tissue, because the first patchy acanthosis has flattened out most of these. While this condition persists in the wart, and it only contains a small number of very much elongated, thin papillæ, the number of papillæ in the Condyloma is ever increasing with its growth. From the primitive or main papilla, there come a number of new, smaller ones, which are furrowed out from the former by the budding epithelium. This constant branching is only rendered possible by the fact, that the main papillæ have, by the abundance of blood and lymph, the new formation of young cells and the emigration of leucocytes, considerably increased in volume. They thus undergo, partly a chronic hyperplastic inflammation, partly a constant folding and division by the growing epithelium, and thus the definite number of papillæ is ultimately greater than it was before the formation of the condyloma. An independent growth of the papillæ into the epithelium, as suggested by the frequently used, incorrect name "papilloma," never occurs. For the recognition of that, it would be necessary to find, as in the hair papilla, a group of connective tissue cells, undergoing rapid mitosis, adjacent to an epithelial tap, and causing a hollow depression in it.

In opposition to the regularity of the dry wart, the irregular formation of Condyloma is, lastly, induced by the succulence and the marked swelling of the connective tissue, and of the uncornified epithelium; the direction of growth is not limited, nor in one direction, from below upwards, but is unlimited, in all directions. The external form of the Condyloma is as varied as the inner formation. If the horny layer is firm enough to clothe continually the swollen lumps, it acquires a mushroom or pear-shaped form; this, though a rare form, is the simplest. Usually the external remains of the horny layer soon give way, the horny layer penetrates into the depressions between the larger root papillæ, and leaves, when it falls off, a "finger-and-toe" form of the Condyloma, in which the individual fingers correspond to the root papillæ.* If the horny covering of the latter also give way, and the horny layer penetrate into the younger epithelial buds, and between some of the newly furrowed papillæ, there results a still more complicated, cauliflower surface, when the horny layer falls off. The external furrowing of the Condyloma, *i.e.*, the number of the externally visible lobules, thus mainly depends on the more or less deep penetration of the horny layer into the centre of the epithelial ridges, and on the yielding of the external horny lamellæ, and therefore does not

* To this corresponds the bursting of the ordinary wart in its third stage.

necessarily correspond to the number of root or secondary papillæ. There are almost always fewer external lobules than papillæ.

The characteristics of the Condyloma, by which it may always be distinguished from Verruca vulgaris, are consequently the following :— the thin horny covering and absence of hyperkeratosis, the remarkable size of the prickle cells and the inter-spinal spaces, the numerous and ever-present mitoses, even in the upper prickle layers, the complicated furrowing of the surface, the constant active dilatation of the vessels, which later gives place to a regular chronic inflammation, with cell formation, leucocytic emigration, and abundant sero-fibrinous exudation, and finally, the persistent papillary furrowing by the growing epithelium.

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All these works are of little value histologically. Roser's inflammatory Cutaneous Papilloma, in which, from oblique sections, he described "the growing together of club-shaped swollen papillary ends," would comprise all a-typical epithelial growths, in all sorts of ulcers. And the statements of the text-books on the histology of Condyloma, even in one otherwise so precise as that of G. Simon, are strikingly weak. The oldest investigator, Lebert (1845), correctly described Condyloma as an epithelial growth, and was on these grounds attacked by G. Simon. By the maintenance of the definition of Papilloma, the comprehension of all acanthomata would be completely obscured.

Epithelioma contagiosum.

Epidermic tumours, the size of a mustard-seed to a pea, projecting semispherically, hard, smooth, yellowish-white to mother-of-pearl in colour, somewhat transparent, often dimpled, which appear in children mostly on the face, in adults on the genitals, spread by auto-inoculation, and often occur in small epidemics, especially in schools. Retzius, in 1872, proved their contagiousness by successful inoculation. Vidal, in 1887, had the results of his successful inoculation figured in the well-known cast of Baretta, and thus convinced the scientific world of the contagiousness of the affection. The striking elastic hardness of the nodules makes the name molluscum, which they have long

retained, quite inapplicable, on account of its confusion with Bateman's "molluscum"; I therefore prefer the name Epithelioma contagiosum of Virchow and Neisser. The nodules are only soft when one has, by pressure, squeezed out the contents, in the form of a hard, small white body. Possibly at the commencement the word "molluscum" did not indicate a soft tumour, but the idea has attached to the expression; this growth should therefore be emancipated from the term "molluscum," and the colloid degenerated epithelia present in it from the term "molluscum bodies."

Considering the small size and clinical significance of this epithelioma, it has, even histologically, an unusually extensive literature. The shape of the small tumours, when freed from their covering, recalls the form of a sebaceous gland, and this led, in earlier times, most investigators to regard them as degenerated sebaceous glands, or at least to place the original seat of growth in the follicular epithelium.

A formidable series of investigators, with Virchow, Rindfleisch, Bisiadecki and Renaut at their head, have maintained this follicular development, or regarded it as probable. Among the dermatologists who adhered to this view (among them Hebra, T. Fox, Hutchinson, Fagge, Thin, Crocker, Zeissl), Kaposi still maintains it to be correct. But a large number of other investigators have denied its follicular origin, and derive the tumour, either from a proliferation, with degeneration, of the surface epithelium (O. Simon, Caspary, Geber, Lukomsky, Boeck, Bizzozero and Manfredi, Campana, Török and Tommasoli, Kromayer), or from the immigration of (animal) parasites, which lead to proliferation of the surface epithelium (possibly Retzius and Klebs, and definitely Bollinger, Darier, Vidal, Leloir, and especially Neisser).

It is very easily seen, how the apparent, acinous form of the small tumour, advancing from the epidermis to the cutis, has led to its comparison with a degenerated sebaceous gland. But it is not so easily seen, how, in an investigation specially directed to the point, anyone could remain long in doubt, and quite incomprehensible how, with our present histological reagents, anyone could ascribe its origin to a sebaceous gland. For the first necessary for such an assumption, the presence of remains of sebaceous glands in the small tumour, and the second necessary, the existence of transitions between sebaceous gland and epithelioma, are never present, and have never been recognised. While in charge of the official examination of prostitutes, I had ample opportunity of studying this condition, and have, in the investigation of several hundreds of sections, never found the remains of a sebaceous gland, or anything like a development from one. In this point I must confirm Boeck, Lukomsky, Neisser, and the other defendants of the development from the surface epithelium. Now and again, though rarely, we find a lanugo hair, with or without its sebaceous gland,

laterally attached to a nodule, or even centrally enclosed in a node consisting of several small ones. But even here, no special relation of the epithelial growth to the gland or the follicle can be discovered. In fact it is remarkable how rarely this contagious affection is localised at the exit of a follicle, for, in general, this point is especially liable to contagion. So that, even if it were possible to recognise, in an individual case, the origin of a nodule from the prickle layer of the follicle, it would have no significance for the general origin of the tumour.

On the other hand, we find everywhere, on examining the just visible nodules around older ones, the most evident proofs of the commencement of the growth in the prickle layer of the surface. At first, a single round projection is depressed pretty perpendicularly downwards, and the papillary body beneath it flattened, or the papilla is pushed to a side and diminished in size. The same takes place on a few neighbouring places, and the projections run together, by enlargement, into a small acinous structure. The smallest nodules have, however, a flatter form. But since the further increase does not take place by the addition of new centres of proliferation in the neighbouring epithelium, but by the further proliferation and formation of secondary projections from the first ones, the nodule separates itself, as a uniform lobulated structure, from the rest of the completely normal surface epithelium, and extends downwards, as a semi-spherical, much-folded and tightly packed epithelial mass, greatly distending the surface epithelium of the neighbourhood, and thinning the cutis beneath it.

I have intentionally used the word projection* for the epithelial protuberances, meaning to indicate that they are never long and thin like ordinary epithelial taps, but always short and strikingly round.

The reason of this lies in the fact, that the epithelia not only simply proliferate and thus retain their size, for then they would only form a uniform mass, which, from the varying resistance of the cutis, would have the form of ordinary ridges and taps, but some of them swell up enormously, and the affected epithelial area is spherically enlarged and projected. In order to make this distinction quite clear, we have only to consider the difference in the form of the purely epithelial taps, proceeding from the sides of the hair follicles, and of the sebaceous lobules proceeding from the sebaceous glands. In the sebaceous glands, also, the round lobular branching of the gland is due to the fact, that, in addition to epithelial growth, distension of certain central cells (by fat) takes place. If all the cells of epithelioma were equally distended, there would be no formation of lobules, but the swollen epithelial mass would be a uniform round body, like an epithelial cyst or vesicle. But what occurs is, that only certain areas

* *Buckel*, literally a hump.

of the prickle layer show growth and distension, while parts between them remain inactive. These, of course, arrange themselves concentrically around the swollen areas, are arrested in development by the distension of the latter, and form the lateral angles of the lobules. In the smallest nodules, the arrangement of the projections is pretty irregular, but the more the whole structure grows in all its parts, and the greater the pressure becomes inside it, the more regular forms do the closely-packed protuberances attain, and they are often completely compressed together, and the connective tissue between them gone. The connective tissue septa, which are frequently—but by no means always—found between the external protuberances of the growth, only exceptionally correspond to original papillæ, for the papillary body has usually been flattened and depressed beneath the small nodules. Only where several primary nodules accidentally develope, at the same time, in neighbouring epithelial ridges, does a papilla persist as a septum, and sometimes contain a blood capillary.

The mechanical principle of growth, which characterises Epithelioma contagiosum, may consequently be ascribed *to a growth and simultaneous swelling of scattered epithelial areas, under external limitations of space.** Since it is the same principle of growth, which induces the acinous form of every sebaceous gland, we cannot deny a certain analogy between them. But there is no question of a genetic connection.

In regard to the second question, whether a peculiar epithelial degeneration, or animal epithelial parasites induce the peculiar forms, which have been found in the tumour since the time of Henderson and Paterson, we have to study those enclosures in the epithelia, which cause their swelling. Anyone, who is not familiar with these "peculiar globes," may be recommended to make a few, very simple stains in definite sequence, which, without anything further, permit of definite conclusions as to their nature. For this, sections of tissue simply hardened in alcohol, suffice.

Certain facts have all along been seen quite clearly with the familiar simple hæmatoxylin and carmin (picro-carmin, picro-cochineal) stains; we shall begin with those. Here, even with a low power, we can distinguish a central horny plug from the radiating, non-cornified lobules of the epithelioma, by a deeply-stained zone of kerato-hyalin (and also elëidin), which surrounds the lobules like a girdle; their contents pass above usually into a common horny plug. The kerato-

* Very interesting in this connection was an abnormally formed preparation which I got in 1878, and still possess. I found, along with many other nodules, one strikingly long one, which, after excision, resembled a flat pod, six millimetres long, and which had developed in a pre-formed cavity. It had the ordinary structure. There was no formation of lobules, and it was only indicated by a slight infolding of the otherwise smooth surface. No one would have suggested its origin from a sebaceous gland.

hyalin is especially abundant, and in the form of coarse granules, and these are reticularly arranged, enclosing light, unstained, oval or spherical structures. Above, these structures are surrounded, inside the under part of the horny plug, by a net of elëidin drops. We note further, that the whole horny plug consists, not of ordinary flat, wavily arranged horny cells, but of oval, pretty equal horny capsules, which are more loosely arranged than usual, and each of which encloses an oval, unstained, very refractile body.

These peculiar bodies, which distend the horny cells into oval capsules, and are sheathed in the marginal zone by the kerato-hyalin and elëidin of the transitional cells, are the questionable structures whose origin we are investigating. No doubt in these preparations we do not see many of them, until we examine the zone of the granular layer; we only note certain faintly-stained, cloudy parts, in the already enlarged prickle cells, which evidently pass into the structures in question. But these preparations show us, definitely, that the process of cornification of the prickle cells, in spite of their altered formation and in spite of the strange enclosures, takes place quite normally, through the stages of granular and elëidin-containing basal horny cells, as it does in normal surface cornification. I have long and repeatedly drawn attention to the fact, that this behaviour of the epithelia is a striking proof of my theory of cornification, according to which the whole process takes place on the surface of the cell only, and a co-action of the cellular contents is unnecessary. Here the contents of the cell are pathologically altered, or used up before the formation of the kerato-hyalin, and yet we have as usual the cornification of the outer surface, while kerato-hyalin and, later, elëidin are deposited between the horny wall and the foreign contents of the cell.

But we learn more of the origin of these bodies in sections with a *good protoplasm stain, i.e.*, with alkaline or best of all polychromatic methyl-blue, and decolourisation with kreosol, styron, or with glycol or glycerine-ether mixture. The two latter methods have the advantage of the former, in showing both the horny cells and their contents, which, with the two former methods, retain too much methyl-blue. We now see appearing, even in the lowest rows of the prickle cells, the predecessors of the oval bodies. The affected prickle cells swell up by the increase of their stainable protoplasm, which is here dark blue to blue violet, and this is collected at one pole of the cell, frequently, but not always, the distal, so that we usually see, at one side of the large vesicular nucleus, a deeply stained, very granular, and on the other an only faintly stained, more homogeneous mass of protoplasm. It is in the deeply-stained segment of the cell that the first pathological changes appear. A slight greenish tone pervades the blue violet, while the

dense granulation disappears, and the affected part of the cell becomes more homogeneous. We see only a few cells at this stage; those immediately beyond them are usually much more affected. In them, almost all the protoplasm is converted into a greenish, homogeneous mass, inside which the bluish violet protoplasm stain still adheres to a net of granules and threads; this is usually attracted to one side of the cell, so that the nucleus comes to lie at the cell wall, which is distended and thickened into a very large oval capsule. Thus one pole of the homogenised cell is always denser than the other, and only the former retains the persistent granular protoplasmic net, inside the homogeneous substance, while at the other, the alcohol has induced a shrinking of the more fluid contents, with retraction from the firm cell wall. Thus there develope, at these usually proximal ends of the cell, a few vacuoles, which have no pathological significance.

In those preparations where both the horny layer and the keratohyalin are decolourised, *e.g.*, by glycol, we see the homogeneous clumps of the lowest prickle layer passing, without any sharp margin, into the oval bodies of the horny layer. The remaining blue protoplasmic net in each homogeneous clump is gradually more faintly stained, and finally no more than indicates the lines of separation between the facetted little clumps, into which the larger ones have broken down. Where true cornification commences at the outside of the cells, these latter somewhat contract, and the cell mantle now closely encloses, in addition to a hardly recognisable remnant of the nucleus, a group of six, eight or ten homogeneous fragments, with facetted borders, which, with other stains, seem to form uniform, oval bodies. The lines of separation between the homogeneous flakes are certainly less numerous than the threads of the protoplasmic net in the lower prickle cells, and the homogeneous flakes of a horny cell are much less in number than the homogeneous clumps of the prickle cells. But since this net is protoplasmic in nature, and the endoplasm of every epithelial cell disappears in cornification, or at least no longer stains, the reduction of this protoplasmic remnant, in the complete horny body, is not remarkable, any more than the corresponding conjunction of several homogeneous clumps into a larger and firmer homogeneous flake.

It is therefore very probable, that a part of the protoplasm of the prickle cells is converted into a colloid mass, while a much smaller part remains reticular, so that, while cornification takes place normally on the outside of the cell, and the nucleus as usual diminishes to an unimportant remnant, the dilating cellular contents are transformed into a group of distinct, but closely packed colloid fragments. But nuclear, kerato-hyalin and protoplasm stains can only approximately, only negatively define the true nature of a colloid body; a specific

stain is necessary to confirm the existence of *colloid and hyalin substances.* We know that these stain very deeply with acid colours, *e.g.*, with acid fuchsin, which is also a contrast stain to methyl-blue, the best stain for the protoplasmic parts of the epithelia. The best method is to treat sections, deeply stained in alkaline methyl-blue, with a dark red solution of acid rubin, in a concentrated solution of tannin.

In such sections the colloid substance shows selective staining. It may be followed easily with a low power, from the reddish stained poles of the lower prickle cells, to the ruby red bodies of the upper horny layers. We see a beautiful double staining of the distended cellular contents; the colloid clumps are at first found enclosed in a dark blue net of protoplasm, which gradually, but never completely disappears, and, even in the complete horny cell, surrounds, though in reduced amount, the oval colloid bodies. We further see, with this double stain, the dense ecto-fibrillation of the colloid epithelium, as a reddish membranous shell, even in cells which still lie in the lowest prickle layer. This thickening of the outer wall only appears in those cells which suddenly increase very much by swelling of the cellular contents; it is therefore only a phenomenon of compression. We see that there is here no cornification, by the much later appearance of kerato-hyalin in the upper prickle layers.

We see the relations of the prickles and the epithelial fibrillation, still better in sections which have been counter-stained with hæmatoxylin and—ignoring more complicated stains of epithelial fibrillation—I would recommend the following very handy stain, as especially useful. The sections are treated for ten to fifteen minutes in a 1% solution of acid fuchsin, and then differentiated in ordinary alum hæmatoxylin solution. We then see very clearly the colloid changes of the epithelia, and their relation to the outer wall of the cells. It is evident that the connecting bridges of the cells are everywhere well preserved, even where the prickle cells are swollen. But the occurrence of loosely packed horny cells shows that, in the distension of the prickle cells, a loosening must have taken place, such as necessarily follows, on physical grounds, the globular distension of cubical bodies. But this tendency to lateral solution is overcome by the firm net of epithelial fibres, and the cornification of the outer wall of the cell is not in the least affected by the marked changes inside the cells.

These four stains, for kerato-hyalin, protoplasm, hyalin, and epithelial fibrillation, amply suffice to study the development of the peculiar bodies, which are nothing more than hyalin or colloid prickle cells. What distinguishes this hyalin degeneration from other forms of hyalin epithelial metamorphosis (*e.g.* in carcinoma, Darier's disease), is the exclusive affection of the interior of the cell; usually it is the

ecto-fibrillation, here normal, which undergoes hyalin degeneration. This integrity of the horny armour of the prickle cells has contributed much to the ignoring of the idea of a degeneration of these cells, and to the favouring of that of a parasite in the cells ; but the reason does not suffice, for we are accustomed to see, in this very hyalin metamorphosis, a sharp, and often capricious limitation of the process. Bollinger's theory of the coccidial nature of the oval bodies, which has been maintained especially by Neisser, has been peacefully interred by the careful investigation of Tommasoli and Török, and has therefore only an historical interest. These authors showed, on the one hand, that the structures in question presented no appearances of life, and that, on the other, the younger stages of the metamorphosed cellular contents were affected as little as the older ones, by the strongest caustic alkalis and acids, thus proving their colloid nature. When, in spite of this, Neisser still maintains the coccidial nature of the bodies, as the most certain part of the theory of psorospermosis, he only demonstrates the absolute want of foundation for the whole theory, so far as it applies to skin disease. For such a theory everything is wanting, from the first histological recognition of the psorosperms, to their cultivation and successful inoculation, and it is not very evident, why investigators, who follow the footsteps of Koch, should lay so much value on them.

The hyalin metamorphosis never attacks all the epithelia of a lobule, usually sparing the younger cells near the cutis margin, while the cells in the upper layers are, in time, all affected. The more one approaches the horny layer, the fewer intact cells are found, and in the horny plug of an individual lobule, all the cells are always hyalin. We therefore find, on the surface of the skin, in relation to the dimple, only degenerated horny cells, with the exception of those small compressed horny columns which now and again indicate the margins of confluent epithelioma nodules.

The changes around the nodules vary. In many cases they are slight, and there is only a moderate multiplication of the connective tissue cells. In other cases, the vessels around are dilated, and the cells of the connective tissue distinctly multiplied, without the formation of plasma cells ; the number of mast cells is increased, and in the epithelium around, there are numerous mitoses. In yet other cases there is secondary suppuration, which invariably penetrates downwards. In such cases, we find numbers of cocci on the surface and in the suppurating canals, and a purulent crust is formed over the growth. Apart from such evident mixed infections, the search for micro-organisms, inside the horny and prickle layers of the epithelium, has as yet been in vain.

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Acanthosis Nigricans.

This rare affection has as yet only been twice observed, by Janovsky and myself, almost simultaneously (both cases are found in the International Atlas, 1890, Part 4, plates 10 and 11).* It consists of a multiple flat formation of warty prominences, which show on the skin, a brownish-black colour, on the mucous membrane of the mouth and pharynx, a lighter or darker red. In both cases it especially affected the neck, the region of the mouth, tongue and throat, hands and backs of the fingers, the axillæ, the abdominal folds and the genito-crural region, in the female, under the breasts and the large labia, in the male the circumanal region and the mucous membrane of the nose. All stages were found, from a simple, increased epidermic lining, with deepened furrows, to rough, coarsely granular surfaces, and finally to firm, high, condylomatoid papillary growths. The acanthotic regions gradually flatten off into the healthy; and the blackening of the warty structures becomes less towards the healthy margin. My case ended fatally.

Pollitzer, who examined my case histologically, distinguished a Status ichthyosioides (mainly on the hands and neck) and condylomatoides (lips). Further, a few isolated, warty-like structures of the arm

* Since then an excellent work by Mourek (Mon., Vol. XVII., p. 366) has appeared. Conf. also Darier, Dystrophie papillaire et pigmentaire. Annales, 1893, p. 865. (Morris and Pye-Smith have since had cases in England.)

were examined, which appeared to represent a still greater development of the disease.

There were found in the cutis, in sections from the ichthyosis-like stage, dilated blood and lymph vessels, and a slight cellular infiltration with very many mast cells and pigment cells. An abnormal amount of brown pigment is present in the prickle layer, and the uppermost horny layer is coloured diffuse brownish yellow. The prickle layer is somewhat hypertrophied, penetrated by wide lymph spaces, and contains a small number of leucocytes. The granular layer is thickened, the basal horny layer of its normal width. But the upper horny layers are considerably thickened, and induce the ichthyosis-like character of the surface.

In the condylomatoid growths, the inflammatory appearances in the cutis, especially the collection of leucocytes underneath the epithelium, are still more marked, and the blood vessels distinctly dilated. But the main change is an enormous growth of the prickle layer. Just as in acuminate condyloma, the papillæ in the centre of the hypertrophic ridge system are reduced to fine long threads, reaching high into the epidermis, which, after casting the upper horny layer, shows a finger-and-toe form.

The warts on the arm show an extension of the process, so far, that in the very hypertrophic prickle layer, under which the papillary body is completely flattened out, numerous concentrically arranged epithelial masses, similar to those in cancer, are present. The cutis there, is almost free from inflammatory changes. Micro-organisms were sought for in vain.

Other Acanthomata.

There are still several growths of the prickle layer, which do not come under this category, and have not as yet been clinically described. I have often had the opportunity of examining such growths, which had been removed from the corpse, and designated as warts, but which were clearly distinct in their structure from Verruca vulgaris. I might mention especially a large tumour of the penis, which appeared on the skin as a transparent, yellowish, here and there orange-coloured mass, and proved, microscopically, to be a pure, flat acanthoma, without a trace of hyperkeratosis or inflammatory complication. The papillary body was flattened out to an irregular, wavy surface. A systematic investigation of all warty growths would certainly disclose several types of acanthoma.

(b). *Glandular hypertrophy and Adenoma.*

I.—Hypertrophy and Adenoma of the Coil Gland System.

1. *General Review. Hypertrophies.*

The older authors, Verneuil and Förster, did not sufficiently separate the adenomata of the sweat glands from the hypertrophies, or from the carcinomata of those organs. Of the three forms which Verneuil distinguished, the hypertrophy leading to the formation of cysts belongs to the simple hypertrophies, and the ulcerating adenoma to the Carcinomata, so that only the hypertrophy accompanied by budding, according to our present view, deserves the name Adenoma. Lücke does not distinguish between adenoma and hypertrophy; he calls the former, pure glandular hypertrophy, which now and again, but not always, retains the function of a gland. Wagner distinguishes adenoma of the coils from hypertrophy, but less distinctly from carcinoma. In his General Pathology, he noted that the distinction of the adenomata from hypertrophies and malignant tumours is often very difficult.

Thierfelder was the first to attempt to define more strictly, the spiradenoma from the other tumour-like changes of the coils. He rightly laid most weight on the distinct margining and encapsulation of the growth, in contrast to the more diffuse hypertrophies. But further, he believed "that a strict distinction between glandular hypertrophy and adenoma is only possible, if we include under the latter name only those tumours, which, with distinct glandular arrangement of their cellular elements, are in no recognisable connection with normal glands, are therefore circularly encapsuled, and thus, in the strict sense of the word, *heterotopic* structures." In spite of their heterotopia, Thierfelder regards the true adenomata as homologous forms, which owe their origin, like the dermoid cysts, to a process of ensnaring.

According to Thierfelder, then, a benignant, glandular new formation, demonstrably developed from a coil gland, would be no adenoma, on account of the absence of heterotopia. This limitation appears to me too narrow and therefore not practicable, for, in view of the resemblance of so many epithelial growths to glands, we must regard the recognition of pre-existing coil glands, at the seat of the tumour, as the surest proof that we are dealing with an adenoma of the coil glands, and not with an accidental, gland-like acanthoma. I believe then, that—if we are to retain the definition of adenoma—we will, in many cases, not be able to avoid the recognition of homotopia for the

acquired tumours. The case is different in the congenital tumours, for in the disturbances of development of embryonic organs, the local connection with normal ones of the same nature can hardly be required. But here we have, in place of this recognition, that of agreement with the embryonic conditions of the same organ. In fact, Thierfelder's generally too narrow definition would hold for the syringadenomata of embryonic origin (see malformations), though not for the acquired syringadenomata.

In no case can the simple hypertrophies of the coil glands, from enlargement of the coil epithelia, be indicated as adenomata; in this all authors are agreed. Such pure hypertrophies may be found, as Virchow showed, accidentally, in the skin of consumptives, as well as in a great number of progressive disturbances of nutrition, granulomata, and malignant new formations, inside the altered skin or immediately around it, and finally, in many chronic dermatitides. Microscopical investigation, and comparison with neighbouring unaltered coil glands, generally make this quite clear. Usually the lumen of the enlarged glands is dilated, the epithelia are very large and pale, but, with few exceptions (seborrhœic eczema, carcinoma), we find no mitoses. This hypertrophy with dilatation is certainly not caused by stagnation of secretion, not even when—as rarely occurs—we find narrowing of the duct or the pore. On the contrary, nothing is more frequent than the narrowing or complete obliteration of the exit, without any trace of enlargement of the coil epithelia or dilatation of the lumen. But this last condition is not infrequently accompanied by multiplication, by œdema, or by mucous softening of the perispiral connective tissue. This form of hypertrophy is not evident clinically.

The question of separation from spiradenomata first arises in the *pure hyperplasiæ of the coils*, caused by a *numerical increase in the secreting epithelia*. It is not difficult to imagine a definite tumour of the skin, which should consist of a convolution of elongated, rolled up, but otherwise normal glandular loops. For such a condition many pathologists would certainly prefer the name spiradenoma, to the longer one of a circumscribed hyperplasia of the coil glands. But it is questionable whether such has as yet been recognised. The tumours, described as definite tumours of the coil glands, all show numerous changes, in addition to elongation of the glandular loops—namely, division, budding, and transformation into epithelial nests of regular structure,—changes which we certainly cannot regard as simple hyperplasia, for both the original glandular type and the possibility of function are gone. What is necessary for the establishment of the diagnosis of a pure hyperplasia, is, especially, absence of those further changes, and a complete histological resemblance to the normal con-

dition, plus increase in length of the gland, and where the tumour is growing rapidly, the recognition of mitosis in the epithelia. These conditions are not fulfilled by the isolated tumours under consideration; I have only found elongated and mitotic, but otherwise normal coil glands, in the neighbourhood of some carcinomata, and in the stagnatory fibromatosis of the skin.

We might regard a *local increase of the coils, i.e.*, compressed groups of new-formed, complete sweat glands, as an Adenoma, somewhat in the sense of the Polyadenoma of Broca. But such new formation of coils from the surface has, in adults, never been recognised.

It appears to me, then, that we might draw a sharp line between hypertrophy and hyperplasia on the one hand, and adenoma on the other, if we find the criteria of the former in the normal formation and the consequent persistent functional activity of the coil glands. Certainly the general type of glandular formation must not be overstepped in true adenoma, especially for two reasons. Firstly, the membrane, the border towards the connective tissue, must be respected —otherwise we have carcinoma; and secondly, the arrangement of the epithelia must resemble the tube form of the coil glands, and not some other type of epithelium, *e.g.*, that of surface epithelium—otherwise we are dealing with acanthoma of the coil glands. I thus find the positive factor, which distinguishes the hyperplasia of adenoma from simple hyperplasia, in a growth, resembling in structure the coil gland, but exceeding it in architecture, and the negative, in the simultaneous destruction of the normal glandular function, so far as can be histologically recognised by the absence of the normal secretion; in this case fat. The a-typical arrangement of the architecture of the whole new formation is very easily seen in the coil glands, for these are normally formed of a simple, rolled up tube. I believe that every budding and division of the tube, every complication induced by hyperplasia, of this normally so simple architecture, justifies the diagnosis of spiradenoma, so long as the growth is limited by a firm membrane, and does not pass into limitless growth.

2. *Spiradenoma* (*Spiroma*).

There has often been an attempt to introduce the adenoma of the coil glands as a definite form of tumour, but as yet there is no sufficiently distinct clinical characteristic of the Spiradenoma. Especially in France, following the lead of Verneuil, who always tended to ascribe deep lying skin affections to the coil glands, a number of works have appeared on "Adenoma sudoriparum." But, as Petersen has recently shown, none of them show the necessary proofs of the origin of the

tumour from the coil glands. Since Virchow, in his work on tumours, declared Lotzbeck's case to be a confusion with angioma, the tendency in Germany has been to proceed very cautiously with the diagnosis of adenoma of the sweat glands. Thus the definite cases of adenoma of the coils are few.

On the other hand, we owe to Darier the first definite case of epithelioma, *i.e.*, carcinoma of the coil glands (noted in the chapter on carcinoma), while the tubular epithelioma of Cornil and Ranvier is no epithelioma of the sweat glands, but is identical with my cylindrical type of cutaneous cancer. They usually develope from surface epithelium, rarely from the follicles, and certainly not from the coils.

We have first of all to define exactly the term Spiradenoma, on the principles just laid down, *i.e.*, to separate it from simple hypertrophy, carcinoma of the coil glands, and Syringadenoma, *i.e.*, the adenoma of the coil duct. In contrast to simple hypertrophy, the increase of the glandular epithelia in spiradenoma is not associated with retention of the form of the simple winding coil; lateral growths are formed, at first blind, then with a lumen, which, by their tendency to bend and roll up, show that they endeavour to repeat the type of the coil glands. From carcinoma of the coils, the adenoma is fundamentally distinguished by the persistence of the membrane, and the regular arrangement of the epithelia inside it. The presence or absence of a lumen is of secondary importance. For, though the tendency to excavation of the buds is innate in all true derivatives of the coils, the commencement of the growth is always—as in the fœtal condition—a solid tap, and a spiradenoma may thus show, at a definite stage of development, a coil consisting of solid loops. Usually solid and hollow processes are found beside each other.

From the Syringadenomata,* the Spiradenomata are distinguished by the seat of development, which lies there in the duct, here only in the coil. Whether there are other differences in the nature of the epithelia, their extension inside the skin, or their degeneration, between those so closely related tumours, future investigation must show. Probably there are, for it is striking, that the observations hitherto made always indicate a sharp limitation of the seat of origin, which renders necessary the separation of the Spiradenomata from the Syringadenomata.

Of course, in the diagnosis of a Spiradenoma, the histological recognition of the connection with normally formed coils is of great importance. A simple *resemblance* to coil glands does not suffice, even when the coils are completely absent in the affected region. Considering the number of useless and indefinite cases, we cannot, in the future, be too strict in our histological proofs.

* Syrinx tube, narrow duct.

The true cases of Spiradenoma fall into two groups, according as they are accidental accompaniments of other dermatoses, and especially of other tumours, or independent structures, consisting only of adenoma. The latter are as rare as the former are numerous.

The accidental tumour of the coils is most frequently found together with carcinomata and angiomata. I have examined a large series of cancers, in which the hypertrophy, and, further, the adenoma formation of the coils in the neighbourhood, was so striking, that one involuntarily came to the conclusion, which was not confirmed on further investigation, that a carcinoma of the coils was present. The epithelia of the coils multiply mitotically, and enlarge, so that the loops assume unusual forms, and finally show budding. But the membrane does not rupture, and thus the possibility of carcinoma is excluded.

Spiradenomata have often been described in angioma. Waldeyer found, in a tumour the size of a cherry, on the elbow of a child, numerous new-formed glandular coils, in an angioma-like tissue. Petersen described a cystic spiradenoma, which had developed on an angioma, growing outwards from the subcutaneous tissue. It consisted of winding, solid and hollow epithelial cords, which were partly connected with epithelium-clad cysts. As the coil ducts grew into the angioma tissue, some of them were completely cut off.

I have myself been able to recognise a limited adenoma formation in the coils in the neighbourhood of several angiomata, and I have occasionally found it in lupus and in neurofibroma. But typical adenoma formation accompanies the penetration of varices of the leg into the skin (which see). Here the commencement of the adenoma, the budding, is especially well seen. In all these cases the spiradenomata are of course not evident clinically; they are only accidental discoveries. But they are of great importance in the question of spiradenoma, for they teach us what to expect in true, independent spiradenoma.

These expectations have, as yet, only been fulfilled in few cases. The well-known statement of Rindfleisch, which Petersen applies to adenoma (p. 444), relates, according to the author himself, to simple hypertrophy of the coils. His specimens were flat, mushroom-shaped, soft, smooth elevations, not unlike soft warts. The tumour formation was found at the border between cutis and hypoderm, and here formed a cushion, three or four lines thick, which consisted of enlarged glandular loops, partly transformed into small mucous cysts.

The oldest reliable case of independent spiradenoma was published in 1859 by Lotzbeck, from von Bruns' Klinik; although it was not recognised as such by Virchow. It was a rapidly growing tumour, on the cheek of a child, was half

the size of a hen's egg, and showed a central, previously suppurating and afterwards scarred zone, then a middle, red, angiomatous one, $1\frac{1}{2}$-2 lines broad, and an external, greenish-grey one, $1\frac{1}{2}$-2 centimetres broad, ending abruptly in healthy tissue. This striking appearance led von Bruns to diagnose, not angioma, or *at least not pure angioma.*

The investigation of teased preparations showed that the tumour consisted largely of bent canals, as thick as the largest sweat glands, which showed spindle-formed dilatations and constrictions between. In addition to these simple hypertrophic glandular canals, others showed finger or bottle-shaped protuberances, even the formation of clustered acini. These glandular masses were compressed, inside the tumour, into wedges or pyramids, with their apices upwards. Lotzbeck found all the canals, with their appendages, clothed with cylindrical epithelium, whose long diameter was perpendicular to the wall. Only in the canals nearer the surface of the skin, was the cylindrical epithelium replaced by a more flattened epithelium. The lumina were filled, partly with cellular, partly with coarse granular contents. The cells contained one or more nuclei, and often yellowish molecules of pigment. In addition to the epithelia, there were in the canals, numerous small, pale cells, like lymph corpuscles; Lotzbeck says nothing of red corpuscles inside the canals. From this description, it appears to me that doubts of the adenomatous nature of Lotzbeck's tumour are not justified. No doubt the somewhat primitive methods of investigation of the period leave many questions unanswered. But such a gross confusion as that with ordinary angioma appears to be excluded, for Lotzbeck notes that the glandular wedges were embedded in connective tissue, specially rich in small vessels.

The second case, that of Thierfelder, was that of a woman fifty years old, in whom, four years previously, a soft movable tumour, the size of a hen's egg, had developed at the hairy margin of the forehead. It was of the same colour as the skin, and a deep venous net shone through it. When removed, it was found that the tumour had grown into the diplöe of the bone, and had worn it away to the thinness of parchment.

Microscopical investigation showed that, for about three centimetres around the new formation, the medulla of the diplöe was filled with clear, polyhedric epithelia, which so far showed a glandular character, that they had between them, cavities filled with hyalin masses or fat drops. These glandular tubes showed budding, and were of the calibre of the coil glands of the normal skin (35-60μ); the glandular cells had a diameter of 9-15μ, where they were not flattened by stagnating secretion. This led in many places to the formation of cysts $\frac{1}{4}$-5 millimetres in size; in particular, the superficial, older,

outward part of the growth consisted almost completely of cystically dilated, glandular tubes, filled with albuminous fluid, with a relatively small amount of anæmic tissue between. The tumour had no connection with the appendages over it, in particular the sebaceous and sweat glands. Thierfelder regarded it as the product of an embryonic, aberrant germinal gland, which, enclosed by the frontal bone, had grown, first in the bone, and then, thinning the skin, towards the surface.

In regarding the tumour as a true adenoma of the sweat glands, I completely agree with Thierfelder; the winding canal-like structure of the epithelial processes, with the formation of cysts, which do not contain, as in the acanthoma, hyalin masses and horny pearls, but an albuminous fluid, indicates the origin from secreting parts of the coil glands, as the presence of buds and the penetration into the bone testifiy to a great activity of growth. The proof that the tumour proceeded from the bone, appears to me wanting, and the arrangement which Thierfelder notes, that the smaller and younger nests are found in the bone, and the larger and older closely under the surface of the skin (Fig. 1), is distinctly in favour of the origin from the subcutaneous tissue, against a heterotopic development. If, as Thierfelder assumes, the oldest, large nests had originally developed in the bone, and were only pushed upwards, the case would have shown, clinically, a diffuse distension of the bone, and not a nodule, and the outer layers of the tumour would have shown remains of bone. It appears natural to assume that the origin of the tumour was where the oldest and largest nests were found on extirpation, *i.e.* in the hypoderm. Then it would be a true spiradenoma.*

A third case is that described by Knauss—a tumour on the outer border of the foot of an old woman.

Knauss found, in the deepest layers of the cutis, a number of foci, one millimetre in size, which were surrounded by broad processes of fibrillary connective tissue, and contained alveolar cavities, lined by very distinct cylindrical epithelium, with a structureless Membrana propria. There was always a lumen, even where there were several layers of epithelium, which sometimes contained a yellow (Picro-carmin), homogeneous mass. There were transitions from this cylindrically-lined tube, through others with cubical epithelium, to the coil glands of the surroundings, some of whose loops were dilated and embedded in a very nuclear connective tissue. The stroma around was sometimes as cellular as a spindle-celled Sarcoma. Knauss diagnosed a cylindrical epithelioma, with sarcomatous growth of the stroma, and

* I assume, although the author does not state it, that the epithelial tubes possessed independent membranes.

leaves undecided the question of the malignancy of the tumour. In view of the typical glandular, although metaplastic structure, and the distinct Membrana propria, I am inclined, as the author now is, to regard the tumour as an adenoma of the sweat glands.

Another type of spiradenoma is that discovered independently, and almost simultaneously, by Chandelux and the Hoggans, in a form of "Tuberculum dolorosum."

> The case of Chandelux was that of a lady, forty-three years old, who had for six years, in the neighbourhood of the elbow, a subcutaneous nodule, which was liable to spontaneous attacks of pain, and was exquisitely tender on pressure.

The nodule could be divided into a softer, upper part, embedded in fat, which showed numerous blood vessels with oval dilatations, and a dense net of medullated and non-medullated nerves; the seat of the pain was in a hard, yellowish, round tumour beneath. This was about the size of a pea, and showed an extension towards the cutis, where a few hypertrophic coil glands were present. It consisted of a very dense, closely packed collection of epithelial cords, which were rolled and wound round each other. Between them, there was a very little delicate connective tissue. The epithelial cords were covered by a thin membrane, and filled with very regular, polyhedric, angular epithelia. Only those directly seated on the membrane had a more cylindrical form, and stained deeply in carmine, while the central cells, in general, were little stained, and contained hardly visible nuclei. A few of the central cells, which were adjacent to the lateral branches, took a deeper colour. The protoplasm of the degenerating epithelium in the centre was neither fatty nor colloid. Between the glandular loops, very few blood vessels were present, and there were no hæmorrhages. Nerves were not found inside the adenoma, but only, and very abundantly, in the fatty cushion above.

It is not easy to extract the value from the somewhat fantastic work of the two Hoggans. Fortunately there is an excellent plate, which shows more definitely than the description, that the tumour must have been very similar to that in Chandelux's case. It appears here that extravasations of blood, on whose apparent metaplasia in the epithelial cell masses the authors lay much value, had induced a partial destruction of the regular formation of adenoma, so that, in addition to the tubes, unarranged cell masses, of regular polyhedric form, developed, which enclosed the former. Here also the adenoma was encapsuled by firm connective tissue, and the nerves distributed outside.

Finally, we have to note, as a definite case of spiradenoma, that of

Audry and Nové-Josseraud, where the tumours in question appeared simultaneously with other tumours. They were surrounded by a firm connective tissue capsule, and consisted of closely-packed, rolled up, branched bands, composed of two or three rows of cells. The cells were similar to those of the coil glands, surrounded by a membrana propria, and showed, here and there, homogeneous enclosures, which stained yellow with picric acid. In contrast to the cases of Thierfelder and Chandelux, numerous thin-walled vessels ran through the tumours, whose connective tissue septa had partly undergone mucous degeneration.

To these cases I can add one of my own, which I owe to Dr E. Fraenkel. It was a purely subcutaneous tumour, the size of a chestnut. There was no clinical history.

In the skin over the tumour, the epithelium is quite normal, the hair follicles and the very large sebaceous glands are unaltered, and in particular show no outgrowths. But the coil glands immediately above the tumour are enclosed in an abnormally dense connective tissue, and thus unrolled. The consequently isolated and stretched loops show an irregular contour, which depends on the growth of the epithelia inside the membrana propria. Similar loops of coil glands are found singly between the more compact cell masses in the upper part of the tumour. Here they are now and again connected with very long, thin epithelial cylinders, and these latter pass as definitely as possible into the tumour mass proper, while direct transitions of these latter into the coil glands outside the tumour are not to be found. Certainly the preparation before me is only from a small section of the tumour. It is seated in the subcutaneous tissue, has a spherical form, is enclosed by a capsule of thickened connective tissue, and penetrated by broad septa of tissue, with coarse fibres and numerous spindle cells. The tumour lies in the round cavities thus produced, in the form of well-defined areas. Most of the latter have, with the low power, an acinous appearance, so that one would not suspect their origin from coil glands. But we see, between these rounded areas, very long and thin epithelial cylinders, of the calibre of the finest coil ducts, which are mostly arranged in bundles, two to four parallel cylinders, united by cross branches, running into one large area. With a higher power, we find that every apparent acinus may be resolved into a dense lattice-work of very fine cylinders. The latter usually preserve their delicate form, and only thicken at the periphery of the areas, the free ends of the lattice work, where they meet the coarser septa of the stroma, swelling, rolling up and running together.

The acinous appearance of the areas consequently depends only

on the club-like swelling and the confluence of the fine epithelial cylinders, which these everywhere show, where the stroma hinders the further extension of an area. It is therefore most developed at the peripheral areas of the tumour, while many areas in the centre show, almost entirely, the type of a latticed framework, down to the swollen outer ends. The architecture of the largest areas is thus originally that of a regular lattice work, formed by solid, very thin epithelial cylinders, showing no lumina. Only here and there are a few cells swollen and hyalin. No liquefaction takes place. But there are very numerous mitoses in all parts of the area. As the whole tumour is encapsuled by firm connective tissue, the individual areas are also enclosed by a distinct collagenous membrane; but I have not been able to demonstrate a membrane on the individual, fine epithelial cylinders. It seems to disappear when the cylinders enter the dense stroma of the tumour. This shows no inflammatory change, in particular no plasma cells; and mast cells are not present in it.

The diagnosis of Spiradenoma is founded in this case on the integrity of the surface epithelium and the follicular apparatus, on the changes in the persistent coil glands and their transition into the tumour by means of very fine epithelial cylinders, and on the recognition of a basis of fine cylinders in the areas composing the tumour, which show the type of coil glands, though in altered arrangement. An epithelial lattice-work is now and again present in simple acanthomata of the surface epithelium, *e.g.*, in Acanthoma adenoides cysticum, but never so regularly and exclusively as here.

3. *Syringadenoma.*

The unique and very interesting case of this condition is that of Petersen. It was a "Nævus unius lateris" of papillary form, and with a tendency to ulceration, in a girl of twenty. Pieces were excised from the neck and the thigh.

Petersen thus describes the structure of the growths:—"One could trace on serial sections how united ducts of two or three sweat glands ascended; shortly above the coil they increased very much in diameter, and the cubical epithelia passed into cylindrical epithelium; then the ducts began to fork and to show outgrowths, which were sometimes solid, sometimes canalled; these either preserved their cylindrical form, or, more frequently, showed cubical epithelium. Since these structures were constantly increasing by division, and expanding laterally like a broom, the semi-spherical or mushroom form of the individual tumours was developed. It is very remarkable, that

at the border of these new formations, taps and canals may be observed, which show no connection with the structures derived from the complete ducts, but, on the other hand, with the surface epithelium. We thus find a tendency to the formation of glands, a 'miscarried glandular foundation.'"

In a previous work, Petersen noted in other parts of skin from the same case, a connection of the glandular ducts, possessing a membrana propria and a lumen, with the surface epithelium, and therefore had established the diagnosis of a tumour developed from the embryonic antecedents of the coil glands. The coils were normal in all preparations, although often hypertrophic. The connection which I have always assumed between adenoma of the rudiments of the coil glands and of complete ducts could hardly be better demonstrated than by this mixed case.

The tubes of this Syringadenoma are distinguished from those of the tumours yet known, developing from the embryonic germs of ducts, by the fact, that they possess a distinct membrane, in places, cylindrical epithelium, and form no colloid masses; they are by no means, as a glance at the drawings of Petersen on the one hand, and Jaquet and Darier on the other, teaches us, to be confused with one another. The occurrence of this tumour in the form of a unilateral nævus might incline one to regard it as a congenital Syringadenoma. In that case it would require to have a division for itself, and one would have to assume, that, according to the period of development of the embryonic excesses of tissue, importantly different new formations would result. I have, just on account of its marked difference, preferred to leave this case, so long as it remains isolated, with the acquired Syringadenomata.

Certainly I can only place beside it, as a distinct example of an *acquired Syringadenoma*, one single case of my own, that which is referred to in the chapter on gangrene, as *Asphyxia reticularis multiplex*. There I have noted that all the coil glands, with their ducts, were surrounded by an inflammatory cellular infiltration. While in the coils themselves, only some loops show a slight thickening or dilatation in their ducts, as they approach the necrotic parts there is a distinct increase in volume, namely, a widening, a greater winding, and finally a budding of the epithelium, with forked division. The lateral branches given off by the ducts, usually lay closely around them, extending outwards or inwards, inside the surrounding cellular infiltration. But they never form cylindrical epithelium or a free lumen, but represent either solid epithelial cylinders, or are converted in some places into cysts, with colloid, glassy-looking contents. In this they showed a great resemblance to the ordinary congenital syringadenomata.

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II.—Hypertrophy and Adenoma of the Sebaceous Glands.

1. *Hypertrophy of the sebaceous glands.*

Simple hypertrophy of the sebaceous glands appears partly as an accompaniment of other processes, partly as an independent tumour, in which case it forms isolated, indolent, very slowly growing, yellowish-white, non-transparent tumours, the size of a peppercorn to a pea, or larger, reaching semi-spherically above the skin, sometimes, but not always showing the gaping mouths of follicles. The independent tumours are rare, and when present are frequently confounded with Milium, Xanthoma, or seborrhœic warts, and usually only recognised on anatomical investigation; we have only recently become acquainted with their multiple appearance.

Much more frequent is the more or less diffuse hypertrophy of the glands, which chiefly accompanies the chronic forms and results of seborrhœic catarrh, especially of the nose and the middle of the forehead. On the nose, it combines with fibrous hypertrophy to form Rhinophyma, and then produces, on the lobulated growths of that organ, transparent areas, like the glands in the skin of an orange. Then we meet them, not infrequently, in the neighbourhood of carcinomata, especially of the face, even when they develope from the surface epithelium and not from the sebaceous glands, and finally, to a less extent, occasionally, in many inflammatory dermatoses and tumours (Angioma).

There is no object in distinguishing, in the enlargement of the sebaceous glands, hypertrophic changes, in the stricter sense, from hyperplastic, for the size even of the normal sebaceous cells varies very much according to the amount of fat in them. The ultimate size is proportional to the collection of fat drops in the spongioplasm of the epithelia, and therefore, in general, the largest lobules contain

in their centre the largest sebaceous cells. In fact, in every enlargement of the sebaceous glands we have both a hyperplasia and a hypertrophy of the fatty epithelia; in the younger lobules the former predominates, in the older, the latter.

There are greater differences in formation in regard to the implication of the lobules of the gland, on the one hand, and of the infundibulum, containing free sebaceous cells and sebaceous masses, on the other. On this, the local conditions of the sebaceous secretion appear to have most influence, and these are supplied, partly by the local tissue pressure, partly by the activity of the cutaneous muscles. On the nose, for example, where the cutaneous tension and mobility is very slight, the glandular lobules extend by means of new processes, in all directions, press the lanugo hairs, which undergo atrophy, outwards, the coils inwards, and finally fill the whole skin, from hypoderm to surface epithelium, with inter-communicating spherical lobules, of different size. If the majority of them approach the surface, the appearance of the stretched skin is transparent. The infundibula are proportionately small; they are certainly larger than normal, but by no means in the same degree as the sebaceous glands attached to them. They are therefore not particularly striking on the surface, contain, in proportion to their wide glandular surface, only little secretion, and are often seen with the microscope, drawn to a side, or even flattened, and sometimes compressed by the swelling lobules of the glands. In simple hypertrophy of the lobules of the gland, one can see, as well as under normal circumstances, whether a stagnation of secretion exists or not. In the former case the fatty change extends everywhere, down to the last persistent epithelial layer, while, where the secretion is regularly excreted, there are always, at one or more parts of the lobule, several rows of unaltered epithelium. In this first form of hypertrophy, most of the glandular lobules are almost completely fatty, being filled with very large, still unruptured sebaceous cells, in a very inactive condition. Although normally it is very easy to determine mitosis in the marginal epithelium of the sebaceous gland, and we are here dealing with a hypertrophy of these glands, we find none, or at least no more than normal. In addition to Rhinophyma, I have found this form particularly in the neighbourhood of carcinoma of the face.

Hypertrophy looks quite different microscopically, for in it the secretion persists, and the enlarging surface of the gland grows in correspondence. Then the gland, as a whole, shows a sack-like form, such as we usually find in large sebaceous glands, with feebly developed lanugo hairs. To a very large, greatly dilated and deepened main infundibulum, there succeed, streaming outwards and inwards in

regular arrangement, the secondary infundibula, all wide and filled with abundant secretion, all elongated, and with the lobules, at one side at least, showing several layers of non-fatty epithelium. This hypertrophy I have found, in most typical development, underneath certain callous formations in carcinoma of sailor's skin. In favour of the active secretion in this case, was, first, the abundant mitosis, then the active stream of secretion in the ducts which penetrate the thick callosity in the form of very broad pores. We find this form regularly, as an accompaniment of Alopecia seborrhoica of the scalp, where the smooth muscles and the ordinary care of the head still lead to a regular discharge of sebum. But one sometimes meets, here also, the first form in typical development, especially where the mobility of the scalp has gradually become arrested.

The circumscribed hypertrophies of the sebaceous glands in a limited (peppercorn to pea-sized) area of the skin, appear, as already noted, sometimes as single nodules, sometimes as very remarkable multiple new formations on the face. In the first case we have mainly to do with an active multiplication and globular distension of the glandular acini, thus with the first form of hypertrophy. On most of the vertical ones we find no infundibula, but only circular or mutually flattened sections and lateral segments of smaller and larger acini, which are separated by dense, fibrous, occasionally vascular septa with few cells. These represent in the higher degrees of hypertrophy, all that is left of the compressed cutis. We usually find no hairs or coil glands in these growths. Cutaneous muscles are usually still recognisable on the face, but are atrophic. The elastic tissue has undergone pressure atrophy, and is abruptly arrested on the side of the growth. Only beneath the surface epithelium and in the larger septa, are remains of it seen. This, in view of the richness of the skin of the face, the usual seat of these isolated tumours, in elastic fibres, is very evident.

The multiple form of these circumscribed hypertrophies of the sebaceous gland leads to a characteristic eruption on the face, with which Pringle's thorough investigations first made us familiar. Caspary's case was probably identical with that of Pringle. The photograph of the microscopical preparations with which Pringle's work is accompanied, hardly permits of any doubt of the composition of the tumour from sebaceous glands, and only the identification of his case with that of Balzer and Ménétrier, which was a typical *Acanthoma adenoides cysticum*, could throw any doubt on the nature of Pringle's case. I obtained from Dr Pringle preparations of his case, which show it to be quite distinct from that of Balzer, and Dr Pringle kindly authorises this reference, since he himself has recently admitted the identification.

In Pringle's case, the affection, which had lasted from the childhood of the somewhat mentally deficient patient, occupied the central part of the face, the nose and the folds around the nose and mouth, from the root of the nose to the chin, and consisted of indolent, firm, whitish-yellow, smooth, sharply margined tumours, the size of a pin head to a pea, projecting over the surface of the skin ; they mostly stood close together, but were not confluent. The surface was smooth, and there was no indication of the mouths of the follicles. When they were pricked, masses of sebum were discharged.

As Pringle rightly remarks, the sections at once recall the well-known appearances of Rhinophyma, with hypertrophy of the sebaceous glands. He lays stress on the deep position of some of the masses of sebaceous glands, quite beneath the normal level of the base of the hair follicle, which sent processes between the striped muscles of the skin of the face. The number and the position of these masses seemed to him incompatible with the view, that all were combined with hair elements. The small epithelial nests in the neighbourhood of many acini pointed to an extended productive activity of the new growth. In the sweat glands Pringle found no change.

After examining his preparations, I can confirm all these observations, as well as the rest of his description of the tumour, which corresponds to that of circumscribed hypertrophy of the sebaceous glands, mainly affecting the acini. Only at one place (Figs. 1 and 2) does the follicle gape, and a sack-like formation of the gland, with stagnating secretion, is seen. Why I cannot consent to regard the tumour as a true adenoma, will be evident in what I say of adenoma of the sebaceous glands ; the distinction depends on the definition of Adenoma, which I draw more narrowly and sharply.

Clinically, Caspary's case exactly resembles that of Pringle, even to the diminished intelligence of the patient, and the results of the histological investigation of the somewhat insufficient material, hardly contradict the identification of the two cases. But Caspary comes to the conclusion, that the sebaceous glands in his case were distinguished, not by their enlargement, but by their abnormal number. His drawing of the preparation certainly does not justify him in assuming a multiplication of the follicles of the skin, and Caspary appears to understand by "multiplication of the glands," "multiplication of the acini"—perhaps in contrast to the small number of large acini in the healthy skin. Then his description and view would completely correspond to that of Pringle. To me, Caspary's case is, from his description, a *multiple, circumscribed hypertrophy,* not an Adenoma of the sebaceous glands ; any more than Klingel's "fibrous sebaceous adenoma" of the ear.

A short retrospect shows, that we have to do in all these cases with relatively small, indolent, firm, inflammatory, superficial yellowish,

long-standing tumours of the skin, which, sometimes diffuse, sometimes widespread, appear sometimes secondarily to inflammatory and neoplastic dermatoses, sometimes independently, and show a particular preference for the face. In all cases, we are dealing with a growth of pre-existing sebaceous glands, with retention of their normal formation and function, and appearances of compression on all the other structures of the skin, the collagenous and elastic tissue, the blood vessels, coils and hairs. Growths of different form (fibroma, angioma) may be combined with hypertrophy of the sebaceous glands. The distinctions are mainly related to the greater or less implication of the ducts or the acini. In the latter case, the tumour-like character and the compression of the other constituents of the skin are more marked than in the former.

2. *Steatadenoma.*

The answer to the question, whether there is a true adenoma of the sebaceous glands, depends on the definition of the term. There is as yet no recognised definition, and the diagnosis of Steatadenoma is more widely used than that of Spiradenoma. The separation of the Steatadenomata from hypertrophy of the sebaceous glands is, in fact, still more difficult than the separation of Spiradenoma from hypertrophy of the coil glands. There, we can draw a pretty sharp line; for, normally, the type of the coil gland retains the simple tube form, and thus every lateral budding and branching is a proof of adenoma. But in the sebaceous glands, budding is the normal condition; it induces the acinous formation, and any enlargement and multiplication of the acini, greater than normal, is always a simple hypertrophy. Even where the whole cutis is filled with sections of acini, the structure consists only of a simple repetition of the normal sebaceous gland type, in increased degree, and has its example in many physiological changes in the glands. But on the other hand, the definition of adenoma can certainly not be applied, where the sebaceous gland epithelium produces solid bodies, which grow into solid epithelial masses or epithelial cords; we have then some form of Acanthoma, proceeding from the sebaceous gland. The participation of the sebaceous gland in an epithelial growth, proceeding from the follicle or the surface epithelium, is a very frequent occurrence, accompanying the most varied inflammatory and hypertrophic conditions; it is almost a rule, that in every active growth of the prickle layer of the follicle, the sebaceous gland, as such, gives up its function, and its germinal epithelium shares in the general epithelial growth. Where, therefore, solid epithelial cords, even of acinous type, proceed from the sebaceous glands, one is not

entitled to regard it as anything specific to the sebaceous gland, and can therefore not make, with certainty, the diagnosis of Steatadenoma.

> I observed a typical case of this form in an old woman suffering from Mycosis fungoides. She had had for a long time, on the back of the head, an indolent, non-inflammatory, flatly elevated, yellowish tumour, about the size of a shilling, with a swollen, irregular surface.

The very much thickened scalp was seen in this case to be completely filled with epithelial cords and masses, of the most varied form, which all proceeded from the large and sometimes very hypertrophic sebaceous glands. Many were cylindrical, others rosette-shaped or acinous, still others were reticular, and partly recalled the epithelial masses of Acanthoma adenoides cysticum. But they showed neither colloid nor fatty metamorphosis, but, on the contrary, horny pearls in the centre, and had consequently lost their sebaceous gland character. Thus it was a simple *Acanthoma of the sebaceous glands.**

It thus appears as if we must abandon the definition of Steatadenoma in the strict sense of the word, since the benignant tumours of the sebaceous glands are either hypertrophies or Acanthomata of the sebaceous glands, according as the specific character is preserved or not.

But there might also be tumours occupying a median position between the conditions just mentioned, in that, for example, solid bodies first come from the sebaceous epithelium, which, after they have developed in a tumour-like fashion, again recall their point of origin by fatty degeneration of their cells. Then we would have a *growth in a new direction*, agreeing with the definition of an adenoma, if we retain it, and at the same time the proof that the cells of the growth had *not lost* their character as sebaceous cells, during growth. Or there might develope, instead of the true sebaceous metamorphosis, other forms of fatty metamorphosis; but the masses in question must not show the products of the ordinary Acanthomata and Spiradenomata, *i.e.*, horny pearls and colloid masses. If no such tumours were to be found, then it would be better to abandon altogether the term Adenoma of the sebaceous glands. For if anyone attempted to apply it to peculiar forms of simple sebaceous hypertrophy, *e.g.*, to such cases as those of Pringle and Caspary, it would be impossible to draw the line, and we would have to call every enlargement of the sebaceous glands, an adenoma.

But there is the case recorded by Bock, which agrees with the following strict definition of Steatadenoma: *benign, tumour-like growths,*

* I must also regard N. Walker's case of Iododerma as an Acanthoma of the sebaceous glands, and not as a Steatadenoma.

of irregular formation, proceeding from the epithelium of the sebaceous glands, in whose outgrowths, fatty, but no colloid metamorphosis takes place.

> It was a fine granular tumour, eight centimetres long, six centimetres broad, and three to five centimetres high, which was seated on the scalp of a woman of seventy. It had existed since childhood, as a lump the size of a pea, and had only recently grown.

The tumour consisted of glandular lobules, one to six millimetres and more in diameter, imbedded in a partly loose, partly fibrous connective tissue, and showing a sharp margin. The lobes were divided by fine septa into smaller lobules, which further showed a membrana propria. In the interior of the lobes were seen either sections of infundibula, or masses consisting of fattily degenerated cells, free drops of fat, and concretions. With a high power, the concretions showed a distinct concentric arrangement; under a polarising microscope, double refraction, and on the addition of sulphuric acid, the appearance of crystals; they consequently consisted of carbonate of lime. The glandular cells were all polygonal, and had a large nucleus and two nucleoli. They were, at the periphery, closely compressed, but became larger towards the centre, "always showed distinctly their epidermic character and fatty colour." This change could in many acini be followed up to the formation of fatty drops and indistinct crumbly masses. The preparations showing the transitions into the normal skin, were very clear as to the type of the tissue. As a rule, the sweat glands close to the hairs were completely normal, but the infundibula of the sebaceous glands were very much dilated, and filled with the same masses as were found in the interior of the acini. The development of the glandular lobules took place from below upwards; at the convex part of the surface there were no infundibula, while they were present at the base of the tumour, at the margin towards the healthy skin. Bock founded the diagnosis, Steatadenoma, on the triple recognition, first, of the normal behaviour of the sweat glands, second, of the absence of cancerous processes, and third, of the presence of acini, which, in their development, evolution, fatty degeneration and calcification, corresponded with sebaceous glands.

In view of the definition given above, as distinguishing it from simple hypertrophy, it is to be noted of Bock's drawing, that the lobules of the tumour have a much more irregular form than those of hypertrophic glands, and that the whole formation therefore more recalls the Acanthoma adenoides cysticum of Brooke, while the fatty and calcareous degeneration, in the centre of the larger lobules, as clearly distinguishes the tumour from that and Spiradenoma, as it

makes probable its sebaceous origin. Certainly one must admit that this origin would have been still clearer, if, at the more recent parts of the growth, a true formation of sebaceous glands had been recognised, with a reticular spongy character of the cell protoplasm, as in the fatty change in true sebaceous cells. This point must be borne in mind in the future investigation of tumours of this sort.

Possibly—to judge by the clinical resemblance—we must also recognise in the case of Rindfleisch, which he described as hypertrophy of the sebaceous glands, an Adenoma. It was an isolated, broad-based, hairless tumour, the size of a pigeon's egg, seated on the hairy scalp, which on section appeared like the normal mammary gland. Certainly the surface was covered with numerous openings, corresponding to the mouths of the sebaceous glands, which is rather more in favour of hypertrophy than of Adenoma.

The case described by May under the name Cystadenoma of the sebaceous glands, can hardly come under this category. In a tumour of the scalp, the size of a nut, and covered with granulation tissue, there were found, in a coarse-meshed connective tissue framework, single layers of epithelioid, indistinctly margined cells, around broad lumina. In the latter, there were, here and there, yellowish, shining, debris-like masses, which the author describes as sebum,* although everything in this glandular-like structure—the germinal layer, the form of the cells, the lumen, the contents—contradicts such an assumption. His term, "Cystadenoma of the sebaceous glands," depends only on this assumption. It is more probable that it was a peculiar change of the coil ducts, somewhat analogous to the case of Petersen.

The "calcified epithelioma of the sebaceous glands" deserves a few remarks. We owe our better knowledge of it to a number of surgeons in Nancy, especially Malherbe. This author believes that most of the so-called cutaneous stones are calcified epitheliomata of the sebaceous glands. He bases this view on the three following grounds:—(1) on the origin of the petrefaction from an Atheroma in one; (2) on the enclosure of sebaceous gland tissue in another of his twelve cases; and (3) on the presence of Cholestearin. The first and third reasons are, with our present views on Atheroma, no longer proof of a connection with the sebaceous glands; so there remains to us only the one case (cutaneous stone from the ear of a child), in which some points show the character of sebaceous gland cells. This observation is, in view of the abundant material, too isolated and too uncertain in explanation, to

* Probably it was an alcoholic preparation, as no other method of preservation is mentioned.

form the foundation of a theory of "calcified epithelioma of the sebaceous glands." We shall see in the Osteomata of the skin, that there are distinctly other points of origin for cutaneous stones. The case of Bock, just mentioned, makes it probable, that a definite form of large cutaneous stone of the head developes from the calcification of Steatadenomata.

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2. *Of the Cutis.*

(a). *Connective tissue tumours.*

The connective substance of the cutis, in the narrower sense, consists of cells without specific contents, and further, of fat cells, mast cells, collagenous and elastic fibres. Since we reckon the growths, consisting of fat cells and mast cells, with the stagnatory tumours, and none have yet been recognised consisting of elastic fibres, there only remain those composed of simple protoplasmic cells and collagenous fibres. Of these, we have further to separate, on the one hand, the inflammatory ones, which have already been described under the infectious new formations (Elephantiasis streptogenes and Elephantiasis filariosa, Neck keloid, etc.), and on the other, the non-inflammatory progressive disturbances of nutrition, which, being congenital, we will discuss under the malformations.

The thus narrowed class of pure, acquired, connective tissue tumours comprises two well-characterised groups, that of the diffuse and the circumscribed tumours, *Fibromatosis* and *Fibroma*. The former are much more common, for with them we reckon ordinary *granulation tissue*, the filling up of loss of substance of the cutis by means of new formed, young connective tissue. One might be inclined to reckon granulomatous tissue with the circumscribed form—that is, with fibroma, since most of the defects which it replaces are only of moderate size; but apart from the fact that very important losses of substance may be

filled up by granulation, it appears to me important, that, in granulation, as such, there is no tendency to local margining of the growth, but rather a tendency to uninterrupted advance, which is only arrested by the artificial margin of the loss of substance. Further, we must include here the diffuse new formations of firm collagenous tissue, which often develope on the legs, under the influence of chronic stagnation, it being understood, that this is sharply and definitely distinguished from true Elephantiasis (see beneath). In this case, the *stagnatory fibromatosis* is not to be reckoned with the stagnatory tumours, to which assumption the name might lead. For it is a stagnatory fibromatosis, only in the sense that the stasis induces a true new formation of young and old cellular and collagenous connective tissue, but not in the sense of a simple stagnation of tumour masses.

In these fibromatoses, the normal structure of the skin is importantly altered, the epidermic structures sometimes sharing in the hypertrophy, sometimes being compressed and atrophied. Much more rarely, we have a diffuse new formation of connective tissue, in the form of a moderate but widespread hypertrophy, in which the structure of the other constituents of the skin is, as a whole, preserved, and whose results are, therefore, only a sort of general hypertrophy of the skin. Such we have in partial and general giantism. In relation to the share of the individual constituents of the skin, this has been recently investigated in the disease described as *Acromegaly* or *Pachyacria* (v. Recklinghausen). How far the reasons for this lie in a congenital alteration of the connective tissue, remains to be discovered. Pachyacria may develope from traumata in the early years of life.

The *circumscribed connective tissue growths* or Fibromata comprise those known as *simple Fibroma* and *Keloid;* then we must add the tumour-like growth of the connective tissue of the nerves in the skin, the *Neurofibroma* of Recklinghausen, which has nothing to do with Neuroma proper. On the other hand, the Soft warts and so-called Mollusca, which are often put in this class, are not acquired fibromata, but malformations, and mostly, not tumours of the cutis, but of the epidermis. We have thus to consider in the pure, acquired, connective tissue tumours:

(aa). *Fibromatosis.*	(bb). *Fibroma.*
Granulation.	Fibroma simplex.
Stagnatory fibromatosis.	Keloid.
Pachyacria.	Neurofibroma.

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(aa). *Fibromatosis.*

Granulation tissue.

The commonest function of the cutaneous tissue, which is to be regarded as a progressive disturbance of nutrition, is the formation of granulation tissue, after any kind of defect or lesion of continuity. It serves to replace the lost area of skin, and passes gradually, but invariably, into firm scar tissue. The latter is never so fully developed in all its constituents as the normal skin, and is therefore described under the regressive disturbances of nutrition, with the rest of the atrophies. But it would not do to place the first act of the second intention there. For in it there is a very active progressive change, which produces macroscopically visible masses of tissue, in much shorter time than the tumour-forming infectious inflammations are able to do, and which, in regard to the intensity of its proliferative and nutritive activity, is only comparable to some rapidly-growing, malignant new formation.

In addition to this peculiar vigour of growth, shown histologically by the very hypertrophic forms of its elements, the granulation tissue has a special interest, since it occupies a place, in Virchow's work on tumours, beside the young spinal cord, as the prototype of the infective "granuloma," which owes its name to the resemblance. Since then it has become customary, in describing the latter, to use freely the expression granulation tissue. Now there is no doubt, that there is a series of these infectious inflammations which show, exactly as in the healing of wounds, a young, productive, developing, and an atrophic, regressive phase, and that we have in such cases, in the first stage, similar appearances to those in the granulation, *i.e.*, a collection of hypertrophic cells, with proportionately small and soft inter-cellular substance. But a closer comparison of the elementary parts in both cases shows, in addition to many similar symptoms, so many distinct and characteristic differences, that one can only rarely speak of real granulation tissue, in affections of this nature.

Secondly, the historical development of the definition of granuloma makes the knowledge of the composition of granulation tissue of the skin very necessary. It is certain, that by the study of this predominant productive function of the cutis, so varied in its simplicity,

our knowledge of all the forms of cell and inter-cellular substance, in the so-called granulomata, will be advanced.

In the pre-Listerian period we understood by second intention something very different to what we now do. Previously, we were familiar with a wound, which was about four days unclean, from superficial necrosis of the borders and the growth of micro-organisms, and which later, after its "cleansing," *i.e.*, after the throwing off of the necrotic zone, suppurated more or less. The formation of granulations was consequently a most complicated proceeding. Thiersch distinguished a superficial pyogenic, and a deeper plasmatic layer of the surface of the wound, of which the former was due to the breaking down, the latter to the organisation.

In the present aseptic era, only the plasmomatic layer remains as an important constituent of the granulation. A pyogenic layer over it is rightly regarded as an unnecessary complication. Thiersch's method of skin grafting now provides us with any quantity of pure, uncomplicated granulation, and to this, and the kindness of Dr Sick, I owe an abundant material, representing all stages of granulation, with the exception of the very first. On this very early stage, and also on the important question of the first vascular budding, studied by Thiersch, this material permits of no conclusion. I will therefore confine myself to the description of the structure of the complete granulation.

The younger granulations consist mainly of a collection of plasma cells and hypertrophic spindle cells, which are held together by a transparent, faintly fibrillary inter-substance, and are permeated by blood capillaries, which run perpendicular to the surface. This uniform layer grows from remains of the cutis or the hypoderm, into which it very gradually passes. With a simple protoplasm stain, and even with a collagen stain, the margin is blurred and difficult to recognise. But an elastin stain demonstrates the lower, often wavy margin of the new formation. For it is always free from elastin, while the older parts of the cutis show remnants of it, which are always found somewhere in extensive granulations, and occasionally in peculiar forms, as loops, coils and tendrils, pretty high up in the granulations.

The plasma cells at first lie closely together, and are of considerable size. They lie most closely around the blood capillaries, the spindle cells being more evident in between. It is seen at once, that the small plasma cells, with characteristic nuclei, and fine, very deeply stained protoplasmic borders, which play such an important rôle, especially in lupus, are completely absent. Especially towards the surface, there is a great number of plasma cells, with irregular, nibbled borders. Indeed, on closer consideration, we see that most of the plasma cells

are slowly breaking down. In those which are deep and nearer the vessels, there are only a few indentations and small protuberances of the surface. But further outwards, most of the plasma cells show all forms and degrees of breaking down, so that the nucleus is partly or completely bared at one side, and the cell finally consists only of the characteristic, coarsely granular nucleus, and a deeply-stained, irregularly-shaped remnant of protoplasm. Finally, we find also completely naked plasma cell nuclei, which are always easily distinguished by their formation, from the few leucocytes. Indeed, even when these, as is often the case on the surface of œdematous granulations, break down, they are still recognisable as collections of granules. In such places, in addition to dry breaking up, there is a sort of solution of the plasma cells, the granular protoplasm partly disappearing from them and displaying the empty net of spongioplasm. But on the other hand, the formation of plasma cells goes on to the formation of bi-nucleated, very large plasma cells, and to small chorio-plaques with three or four nuclei. Probably the nuclei multiply mitotically; but I have not yet been able definitely to note this, for the mitoses, which are regularly present, lie in cells, which, from their round form, may be plasma cells, but, as the granular protoplasm in them is mostly absent, while the spongy is well developed, may also be spindle cells, which, during division, have retracted their processes. At any rate, the majority of the plasma cells in the granulation do not develope by the division of old ones, but by the transformation of spindle cells, "*in situ*."

In favour of this, is a great number of transitional cells, which can always be recognised. The spindle cells become plasma cells, usually after they have considerably enlarged, drawn in their processes, and the cell body has become rounded and filled, first with faintly, then with deeply-staining granules. Since the plasma cells are mainly arranged concentrically around the capillaries, it may be assumed that it is the ingrowth of the capillaries that converts the neighbouring spindle cells into plasma cells. But since these form the majority in the young granulations, the growth of the granulation at this period is to be attributed, not alone to cellular new formation, but also in a considerable degree to cellular swelling. Apart from the vascular endothelia, hypertrophy of the protoplasm is much more prominent than proliferation.

The spindle cells in the younger granulations play only a modest rôle; they are neither so numerous nor so large as the plasma cells. But they are nowhere completely absent, and indeed they provide the material for the formation of new plasma cells. On the other hand, they are, compared to the ordinary spindle cells of the cutis, very

hypertrophic, and show thick and long processes, which, like the cell body, consist of a very well-stained, distinct net of spongioplasm. With these they communicate with the swollen spindle cells of the cutis around. Evidently their function is mainly to assist the blood vessels in combining the loose mass of plasma cells into a "tissue," for at this stage there is present no firm fibrillary frame-work of the granulation. The hypertrophic spindle cells show distinct and abundant mitosis, and thus contribute to the enlargement of the granulation by proliferation.

While these hypertrophying and proliferating cell masses are arranged in layers parallel to the surface, the new blood vessels run perpendicularly, somewhat obliquely from the sides, and at pretty regular distances. On vertical sections, they represent straight tubes, which consist of flat, large nucleated cells, containing abundant staining protoplasm. Horizontal sections of the granulations, in which the capillaries are cut across, show that they are surrounded by a second and even by a third, pretty regular, cellular tube, and thus appear as so many rings. The external ring passes gradually into the net of spindle cells, in whose meshes, close to the vessel walls, the large plasma cells appear. This sheath of one or two layers of flat cells distinguishes these capillaries from the normal ones of the cutis, as does the absence of elastin and muscle from the larger cutaneous vessels. These capillaries all make for the surface, without sending off any lateral branches. Here they bend, anastomose with one another, and pass into venous capillaries, which follow the same direct perpendicular route back.

We usually find, in the capillaries, numerous polynuclear leucocytes, along with red blood corpuscles, many of them arranged marginally, but not in the act of emigration. This corresponds to the relatively small number of leucocytes which are found in granulation tissue. They are usually only found in any number in the upper layers. They never form collections or abscesses, and do not cover the surface, in however thin a layer, although, in the delicacy of the vessel walls and the traumata to which all granulations are exposed, there appears to be every facility for emigration. But there is evidently no specific leucotactic irritant, and thus the small number of leucocytes which we find in all granulations may also be ascribed to the minimal, unobserved chemical influences, which cannot be avoided even in aseptic granulation. At anyrate, there can be no question of these few emigrants aiding in the formation of the granulation; for their behaviour is quite passive, and they gradually break down, if they do not return to the vessels. Very few mast cells are found at this stage. They are irregularly distributed, not particularly granular, and frequently badly defined.

The most perplexing constituent of the granulation is the inter-cellular substance; it is never exactly the same, either in different cases or in different parts of one and the same granulation. Only so much is everywhere evident, that it consists partly of a fluid or semi-solid substance, and that, in addition to young collagen, it contains much old, dissolving collagen. A thorough collagenous staining of the youngest possible granulations, which are not at my disposal, would be necessary to settle its nature. In many places we see fine fibres proceeding from the spindle cells, which, with a double stain, take, partly the protoplasm stain, and partly the collagen stain, and are to be regarded as the first stage of young connecting substance. But one sees these fibres also apparently free, and sometimes forming nets enclosing the plasma cells, sometimes combining into thin, loose bundles, of wavy or elongated form. Between this very delicate and incomplete scaffolding, there lies a faintly-stained, homogeneous, semi-solid mass, which unites the different forms of cells, fibres and vessels, as if they were imbedded in gelatine. Whether this represents liquefied old inter-cellular substance, or new, derived from exudation and serving as a provisional frame-work, I am unable to say. It is certainly not the product of the cells of this period, for they are all actively secreting protoplasm, and enlarging. In addition to these constituents, we see, especially in the under parts of the granulation, masses of softened and breaking down inter-cellular substance, and in many places this passes, without a sharp margin, into the semi-solid mass, so that the suggestion that the latter is completely liquefied old collagen appears justified.

At all events, so much appears to me to be established, that in the younger granulations the transformation of spindle cells into plasma cells, and the new formation of vessels, are accompanied by a mainly regressive metamorphosis of the inter-cellular substance. Striking, this fact is not, for in most places, the formation of plasma cells is accompanied by a diminution of the collagen. But here we have a general œdema of the altered tissue, which makes the remains of the old frame-work swell up, and possibly also favours the breaking up of the plasma cells. The foundations of a young framework are feeble and irregularly present; they are found best developed immediately around the blood vessels.

I must thus regard the young granulation layer mainly, not as new formed, but as altered cutis tissue, whose remarkable swelling is induced, partly by the solution of the inter-cellular substance, partly by a distinct swelling of the cells, with the accumulation of granular protoplasm. Any actual considerable new formation of cells takes place only in the endothelium of the vessels; of the other tissues

of the granulation, it affects mainly the resting, hypertrophic spindle cells, and these are in such a small minority that their multiplication cannot explain the tumour-like formation of the whole granulation.

The older granulations which are available to me, and are indicated as such, at the first glance, by their partial covering with epithelium, and their containing a considerable proportion of collagen, show a more regular formation than the younger. The new formed collagenous substance is found regularly arranged in layers, parallel to the surface, and is penetrated at pretty regular distances by the vertical blood vessels, which are surrounded by a broad mantle of large plasma cells. These latter form the only remains of the original widespread plasmoma, for the inter-vascular spaces are now wholly filled by new collagenous substance and flat or spindle-shaped cells. Here, collagenous layers and cellular enclosures regularly alternate, arranged almost horizontally over each other, like the plates of a Voltaic column, with the difference that the cell plates of different levels are connected with one another by processes, while the collagenous plates are merely introduced between. While, consequently, the cells form an almost complete net, there exists at this stage, in the cutis, no proper net-work or felting of collagenous fibres. Where the cell plates approach the vessels, they pass into large spindle cells, which bend round into the perithelia of the vessels. We can see spindle cells, which send some processes horizontally between the adjacent collagenous plates, while others follow the vessels perpendicularly outwards and upwards. But on the other hand, we find also distinct transitions between these spindle cells and the perivascular plasma cells, which justify the assumption, that spindle cells with long processes may be developed from plasma cells. Such transitional cells still retain portions of deeply granular protoplasm, an irregular large cell body with short round projections and long processes, in which the spongioplasm is distinctly evident as a net. They are more darkly stained than the rest of the spindle cells.

While in the younger granulations in general, plasma cells predominate, in the older ones, it is the spindle cells. But this word very insufficiently describes their form. The name is most applicable to those areas which are in a state of transition from the younger to the older stage, and in which the cellular œdema has not given place to the ultimate dryness. Here there are found no thick collagenous plates, but delicate bundles of fibrils, which, loose and wavy, occupy the space between the cells. They appear on vertical sections almost spindle-shaped. Yet the large, oval

nucleus is usually pressed to one side, and thus the cell body here is more swollen, terminates bluntly, and usually sends two or more processes towards this side, while the opposite end passes into a single, elongated, pointed process. In these processes it is most easy to demonstrate a direct transition of the spongy protoplasm into a fine thread, taking the stain of collagen; a fibril. Yet it often looks as if these collagenous fibrils did not proceed from the protoplasm net itself, but only came from below it, possibly belonging to a more distant cell; the study of this subtle question is made very much more difficult by the extraordinary length of the protoplasmic processes. Now and again I have found such spindle cells, which at their pointed end have a complete, though small bundle of fibrils, and others, which, in addition, show at their blunt ends several such bundles. But these are exceptional appearances; most of the spindle cells appear to lie passive between the fibrils.

Somewhat older parts show, on perpendicular sections, the same appearance. Here also there appear, between the collagenous plates, spindles, which are elongated on one side and blunt on the other. But horizontal sections show that the true form of these apparent spindles is that of large, wedge-shaped, pointed plates. I will therefore call them *plate cells.* (Front., Fig. 14.) These plates have a regular margin only at their long sides, while at their ends they pass, without any sharp border, into the neighbouring plates. It is the ordinary rule, that the nucleated end is broader and sends off more processes than the smaller, opposite pole. There usually lie, in the swollen end of the wedge-shaped plate, several (two to four) nuclei, sometimes alongside, sometimes over one another. This also is better seen on horizontal sections. If the spongioplasm is sharply stained, we see in many places a uniform surface of spongy protoplasm, which is interrupted by fissured spaces, and in which, swellings, with nuclei and nuclear collections, indicate the cell territories.

The relation of the vascular to the a-vascular areas of the granulation is also very evident on these horizontal sections. The former are distinct, circular or round, sharply margined cross sections, which are all enclosed by the uniform, reticularly arranged, a-vascular part. Inside the former is a series of large venous and small arterial, cross-cut vessels, united by a tissue rich in spindle and plasma cells, into a vascular cord. The older the granulation is, the fewer are the venous and arterial capillaries seen in these vascular cords, but the wider are the lumina and the thicker the walls of those which persist. In the latter there are even formed fine elastic fibres, so that, with an elastin stain, these sections of older vessels stand sharply out from the granulation. It is the only place, where, during granulation, elastin is formed;

in definite scarring, it is, though only slowly, formed everywhere. That, in addition, scattered remnants of old elastin are almost always found, has already been noted.

The leucocytic emigration from the vessels is still more sparing than in the young granulation; but mast cells are more abundant and better developed.

The most problematic constituent of these older granulations is, again, the collagenous tissue. Certainly, perfect staining of the spongioplasm and the collagen is of use in decision. But even these stains alone do not supply a solution of the contentious question, whether the collagen proceeds from the cell body or from a formless inter-cellular substance around the cells, although here it must be settled. I am only able to point out the difficulties, without being able to supply a solution. From my limited material, these are mainly two. The first difficulty lies in the decision of the question, whether the sharply rounded, fibrillary threads, which are distinctly in connection with the protoplasmic processes of the spindle and plate cells, really come from them, or only lie on them. The second, and it appears to me much greater difficulty lies in the answering of the question of the origin of the thick collagenous bundles, which are apparently simply included in the net of plate cells: do they develope from the fibrillary bundles by coalescence and interstitial growth, or independently of them? As we see, the problem is only made more precise, and is still undecided by the newer staining methods.

Only so much is certain, that the collagen of the older granulations, if it develope from cells, can only owe its origin to the spindle and plate cells, for the fibroma formation is everywhere accompanied by the abundant formation of spindle cells, consisting almost entirely of spongioplasm. These only deserve the name of fibroblasts. But there are other points in the structure of this collagenous substance, which is distinctly different from that of the cutis. In this collagen we have isolated, homogeneous plates, which, on vertical sections, appear spindle or wedge-shaped. In many places there is an indication of a composition from finer lamellæ, but they can never be analysed into fibrillæ. On the other hand, they are always covered at one or both surfaces, but only where they are adjacent to plate cells, with a layer of streaked and perhaps fibrillary collagenous substance, which, with various stains, shows a different tinge, and which, consequently, is introduced between the collagen and protoplasmic plate. I suspect that the plate cells pass directly, only into this loose young collagenous substance, and that perhaps it again supplies the material for the collagenous plates.

The plates always show, with a good collagen stain (acid fuchsin,

water blue, orcein), a marked wavy frilling, as if they had contracted from a hyper-extended condition. Probably they are stretched during life, and take this wavy form only after removal and in the alcohol.

The change certainly indicates a high degree of elasticity in these collagenous plates, which perhaps explains the contractility of a scar.

Scarring and cornification of the granulations are considered with the regressive disturbances of nutrition (under Scars).

Stagnatory fibromatosis.

This subject also is very obscure. Nothing is more popular than the idea that the elephantiasic thickening of the legs depends, partly, or it may be entirely on vascular stasis, but we have, for good reasons, treated the true, acquired elephantiasis (nostras) with the infectious inflammations, and regard it as the type of inflammatory fibromatosis. Here we can only have to do with the very frequent cases, in which, without the occurrence of erysipelas, either apparently spontaneously, accompanying a chronic eczema, or after prolonged ulceration of the leg, with or without varix, a general, firm, fibrous swelling of one or more large areas of the skin of the leg developes. Since these dermatoses, which accompany the fibromatosis, do not of themselves tend to produce advancing fibromatosis, we come back, as a rule, to the complicating stasis for an explanation. Of course, cases of fibromatosis of the leg without any accompanying dermatosis would be proof positive; there would then be no other cause than the chronic stasis. But it would still require explanation, why most cases of simple varix are accompanied by thinning and not by thickening of the skin; for we have in all cases a prolonged, more difficult, delayed circulation, with hypostatic hyperæmia. I must admit, that since I have paid special attention to this point, I have in every single case found inflammatory complications, usually eczema or ulcers, and the existence of a pure stagnatory fibromatosis of the leg is to me very doubtful. But if complicating dermatoses are necessary, it may be that they indirectly cause the fibromatosis by permitting the entrance of streptococci. A hardly noticed, stabile erysipelas might be the cause of the fibrous new formation, instead of the more striking spreading erysipelas. Were this so, it would explain the influence of stasis; for inflammatory fibromatosis certainly increases under the influence of stasis (see Elephantiasis nostras, Elephantiasis filariosa).

The study of the literature of elephantiasis brings us to the same result. Everywhere, the stasis appears only as an adjuvant factor, never as the general cause. We may take as an example a well-

known case, which, at the first glance, appears to be the purest form of stagnatory fibromatosis.

> Stromeyer (Esmarch and Kulenkampff, p. 91) demonstrated at the *Naturforscherversammlung* in Erlangen in 1840, a sixty year old peasant, with marked *Elephantiasis profluens ulcerosa papillaris* of both legs. The disease had lasted for several years, and was frequently complicated by erysipelas. The superficial veins on both sides of the trunk were dilated, and formed, around the axillæ, cords as thick as a little finger. The sectio showed, that the *Vena cava ascendens* was closely surrounded by sarcomatous lymph glands, and at one place, $8\frac{1}{2}$ centimetres long, was so narrow, that only a thin probe could pass through it.

Were the "frequent attacks of erysipelas" not mentioned in the history, the case would seem one of true stagnatory fibromatosis.

Still the existence of such seems to me open to discussion; for when we see that, in order to resist the pressure of the hypostatic hyperæmia, new masses of elastin are formed in the skin of the leg, a widespread new formation of collagen, for the same reason, is quite conceivable.

I have taken much pains to aid in the decision of the question, by histological investigation. For, since we know the histology of inflammatory fibromatosis (elephantiasis), a departure from this structure in so-called stagnatory fibromatosis would distinctly point to a different etiology. But in spite of much search, I have procured little suitable material.

In a large series, I was able to find one varix, which was enclosed in firm, thickened connective tissue, the skin over it being free from external complications.

There was seen at the side of the varix, which otherwise showed the usual appearances (see varix), a flat layer of fibrous, new formed tissue, between the cutis and the hypoderm. It consisted of thick plates, like scar collagen, contained few cells, and was completely free from elastin, while the immediate surroundings, corresponding to the pressure of the varix, were particularly rich in elastin. This circumstance permits the definite recognition of the fibroma as an actual new formation, and its sharp distinction from the almost unaltered cutaneous tissue. There was no inflammatory proliferation of cells, either at the seat of the new formation or in the neighbourhood.

Then I twice had the opportunity of studying the thickened skin, several inches away, around ulcers of the leg (from the corpse), which, except for thickening, appeared macroscopically quite normal.

The two cases were similar; the sections were most interesting with an elastin stain, which divided the very much thickened skin into two distinct horizontal layers, the upper, comprising the papillary body

of the cutis, almost entirely free from elastin, the lower, hypodermal layer, unusually rich in it. In the latter, the fatty tissue had disappeared, and the very much dilated subcutaneous vessels occupied most of it. The coil glands were unusually hypertrophic. They formed an almost uninterrupted layer between cutis and hypoderm, and yet the loops in the coils were closely packed and separated by little intertubular tissue. In one of the preparations, there existed only an elongation and widening of the tubes; in the other, there was also a-typical proliferation, with formation of projections, out-growths and cysts, in fact, a regular Spiradenoma. The collagenous tissue around this vascular and glandular layer was moderately cellular, horizontally arranged, and denser than the collagenous tissue of the normal hypoderm, but not nearly so dense as the collagen of the upper layer. The elastic tissue was especially dense towards the cutis margin, and here often rolled up into crumpled masses and balls. The margin itself was a continuous chain of such elastin clumps, some of which lay beyond, in the cutis. The numerous arteries and veins, which, much narrowed, passed this border, immediately lost their elastin, and extended, sometimes obliquely, sometimes perpendicularly to the surface, to form, inside the distinctly enlarged papillary body, branching and winding loops. The sub-papillary vessels were in many places particularly wide, and surrounded by cellular infiltration, which extended into the papillæ and contained numerous plasma cells, and, especially in one of the cases, great quantities of mast cells. To the much enlarged papillæ corresponded a hypertrophic ridge system; but supra-papillary prickle layer and horny layer were thin, and the capillaries reached close to the surface.

The cutis between the hypertrophic papillary body and the elastic hypoderm, was very much thickened, and consisted of horizontally arranged, very firm collagenous fibres, without any admixture of elastin. Round the abundant vessels here, there were found, in both preparations, a good many coarse granules of golden yellow blood pigment, partly in, partly around the spindle cells. The latter were much more numerous than in the hypoderm, and chiefly arranged around the blood vessels; mast cells and plasma cells, on the contrary, were few in number.

Thus we have: dilatation of all the blood vessels up to the papillary loops; collagenous hypertrophy of the cutis, and disappearance of the elastin, these diminishing towards the hypoderm, in which, with disappearance of the fat, the elastin collects; growth of the prickle layer and of the coil glands, and deposit of pigment in a central area, limited to the cutis. Whether this interesting complex of symptoms, although exactly alike in two cases, really represents the appearance of pure, uncomplicated stagnatory fibromatosis, I prefer to leave undecided, in view of the uncertainty of material from the corpse.

Pachyacria.

Acromegaly, or according to v. Recklinghausen, better, *Pachyacria*, because there is no elongation, but only thickening, consists in an increase in volume of the bones and soft parts, especially in the extremities, which is accompanied by degeneration of the muscles, nerves and vessels. The skin is thickened, especially on the face and the ends of the extremities, can only with difficulty be pinched up in thick folds, often shows spots of pigment, and sweats freely. The panniculus is only feebly developed. The hairs in the thickened parts are usually stronger, the nails thick and flat, but not usually widened.

The concurring observations of Marie, Marinesco, Duchesneau, and especially of Arnold, have shown that, except for deep pigmentation of the prickle layer, the epidermis shows no abnormality. But the cutis, as a whole, is thickened, and is formed of very firm, thick, closely-felted collagenous bundles. The hypoderm also is thickened, but solely by increase of collagenous substance, which, in the form of broad septa with numerous spindle cells, surrounds the atrophic fat lobules, and increases at their cost. The walls of the arteries and veins are thickened, and their lumina narrowed. The very thick sheaths of the nerves show a lamellar arrangement, and in their interior, the connective tissue has increased, at the cost of the broad, medullated fibres. Coil glands are present in abundance and fully developed, both as regards the thick connective tissue around, and the narrow, winding coil. The connective tissue sheaths of the sebaceous glands are also strikingly thick.

Altogether, we have a collagenous hypertrophy of the cutis and hypoderm only.

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(bb). *Fibroma.*

It is rather peculiar that the so fibrous cutis has only a slight tendency to form circumscribed fibromata. Fibroma simplex is one of the rarest skin diseases. There is certainly a great number of tumours, which have been ranked with the fibromata under the names, Molluscum, Molluscum fibrosum, Fibroma molluscum, multiple fibroma of the skin, and acquired and congenital Elephantiasis. But on investigation, most of them prove to be growths of some other

form. It is especially to the credit of v. Recklinghausen to have given the so-called multiple fibromata their proper place, and time has shown, that very many cases of so-called Elephantiasis congenita also belong to the class of Neurofibroma. A number of so-called Mollusca and Fibromata mollusca have been recognised as maternal nævi, and as a special variety of this mainly epithelial tumour. These tumours, previously regarded as simple fibromata of the skin, are distinguished by the fact, that they represent a congenital excess of tissue, and therefore come under the malformations.

If we withdraw these from the number of circumscribed fibromatous skin diseases of the text-books, there remains only a small group of true (acquired) fibromata of the skin. This may be divided into *cutaneous fibromata* and *nerve fibromata.* The cutaneous fibromata comprise two groups: *Simple fibroma* and *Keloid.* The former is much rarer than Keloid, and is only appreciated by few dermatologists, such as Taylor and Hutchinson.

The latter regards it as a form of Keloid, a view which I do not share. Both forms are, like all fibromata, benign, solitary or multiple, and evidently dependent on traumata. While the simple Fibroma shows no tendency to recur after removal, this is one of the peculiarities of Keloid. This alone indicates an important difference between the two forms: Keloid represents a tendency of the whole surface of the skin to fibromatous change, while Fibroma simplex does not. It is the duty of histology to explain this difference. It may just be noted, that this more sharply-defined class of cutaneous fibroma only comprises hard, fibrous tumours. The so-called soft fibromata are no fibromata in the stricter sense, and a soft quality should always make one cautious in diagnosis, and suggest Neuro-fibroma or molluscoid nævi.

(α). *Cutaneous Fibroma.*

Fibroma simplex.

Simple fibroma of the skin, as defined above, is a benign tumour, usually appearing solitary, on the upper part of the body and the extremities, which, mainly imbedded in the skin, is only rarely and little elevated over the surface, and never shows extensive processes. The firm nodules are either sharply defined from the surroundings, or pass diffusely into them, in which case we only feel a hardening and moderate thickening of the cutis, without any sharp margin. The surface is smooth, the colour normal or reddish, and never white and shiny as in Keloid. These fibromata develope from severe traumata (blows, bites) or around foreign bodies (splinters). They grow very slowly, are painless, and are not tender on pressure, like Keloid. They neither extend to the hypoderm, nor are they snared off, above the surface of the skin, like nævi.

As the clinical appearances indicate, we have to distinguish, histologically, two forms of Fibroma: the *diffuse* * and the *circumscribed.*

* The diffuse Fibroma, of course, always still shows a nodular marginal form and limited extension, and is thus perfectly distinguished from *flat diffuse* Fibromatosis.

Perhaps the former only represents an earlier stage of the latter. One finds in the diffuse form, on section, the cutis proper widened, harder, less transparent and whiter than normal. The nodes are gradually lost in the surroundings. All the epithelial constituents of the skin are well preserved, but are separated from one another more than usual, by a simple increase in the amount of collagenous tissue. This, without forming discrete nodules anywhere, nestles around the coils and vessels, permeates and widens the adventitia of the blood vessels, the tunicæ propriæ of the follicles and glands, and alters the structure of these membranes so much, that the organs appear to be directly imbedded in the new tissue. The latter never has the composition of the mature collagenous tissue of adults. It consists of parallel, dense cords of fine bundles, which are only indistinctly fibrillary, but are regularly separated by very small cell plates with rod-shaped nuclei, and show between them no elastic tissue. The bundles themselves are usually not cylindrical, but have a long spindle form, and they show no lymph spaces, like the normal cutis. At the margin towards the healthy tissue, the cellularity of the new growth increases, and passes finally into thick vessels of the neighbourhood, closely enclosed in spindle cells, around which the first foundations of the fibrous new formation are evident.

The characteristic of this fibromatous change lies in its adaptation to the enclosed organs, which it only surrounds in broad sheaths, and then in the cellular, embryonic condition of the collagen. While this last character gives it a certain resemblance to Fibro-sarcoma of the skin, it is distinguished from that, at a glance, by the integrity of the cutaneous structure as a whole.

The circumscribed form of Fibroma simplex is, even macroscopically, pretty sharply defined from the healthy tissue around, and shows on section, white, tendonous, indolent, hard nodules, penetrated by transparent lines; it usually extends somewhat over the level of the skin and is movable with it. According as it developes from the upper or under part of the cutis, the papillary body with the epithelium is thinned and stretched, or unchanged, and only slightly projected over the tumour. The fibroma presses the hair follicles and ducts aside, the coils aside and downwards, so that they are stretched, thinned, and may become completely atrophic. Blood vessels are difficult to recognise in the nodule; where they are present, they lie in the few septa of the tumour which are formed of normal tissue. Elastic tissue is only present in minute fragments. The tumour consists almost entirely of a moderately cellular, collagenous substance, which is arranged in coarse bundles, crossing each other at all possible angles. It is not, as in the diffuse form, an active hyperplasia of young collagen,

but a hypertrophy of the individual fibrillary bundles, to the size of the thickest normal bundles and more, which take the triangular or angled form common to the coarser bundles of the normal cutis, but are distinguished from them by their close packing, the absence of lymph spaces between them, and the greater abundance of spindle cells. In the older Fibromata, especially in the centre, the spindle cells between the bundles almost completely disappear.

We have no evidence of the behaviour of the muscles and nerves in these Fibromata. Probably the tumours take their origin from an adventitial vascular growth, of a fibrous character, which remains more localised, and thus leads to greater swelling, compression of the neighbouring organs in the skin, pressure atrophy of the vessels, &c.

In addition to these Fibromata of the cutis proper, there are circumscribed Fibromata of adjacent parts, *e.g.*, periosteum, fascia, nerve trunks, which compress the skin, thin it or even grow into it, and may be confused with cutaneous Fibromata. To these belong a number of the "*painful tubercles*," which are frequently excised but rarely thoroughly examined, and whose sensitiveness is not sufficiently explained (see Neuroma).

Possibly there also come into this class of simple Fibromata, certain rare, multiple tumours of the skin, which up to now have been all regarded as so-called Fibroma molluscum, but which are clearly distinguished from the Neurofibromata by their follicular contents and the occurrence of comedones and sebaceous cysts, and from follicle-containing nævi, by their containing firm, hard connective tissue. Thus Lahmann's chief case, on which he founded his futile critique of v. Recklinghausen's views on Neurofibroma, and his own theory, corresponds neither clinically nor histologically to the Neurofibromata, but probably to the simple Fibromata; as does probably the analogous case of Hilton Fagge. There should be in future, in the class of multiple fibromata, a clinically and anatomically well-defined section for Fibroma simplex multiplex circumfolliculare, which shows only a superficial resemblance to Neurofibroma, and should no longer be confused with it.

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Keloid.

Cylindrical, small, or plate-formed, broad swellings, extending like ridges over the skin, which sometimes show a sharp margin to the healthy skin, and sometimes, with pointed, often branched processes, gradually sink into its level. The latter are found especially at the ends of the cylindrical swellings. The surface is smooth, stretched, even shiny, the colour that of mother-of-pearl, rosy, rarely dark red, the consistence firm. They develope on predisposed persons, in the neighbourhood of every wound, usually after distinct traumata (wounds, stitches), never spontaneously. The apparently spontaneous, isolated Keloid of the sternum is almost always clearly the results of scratching, on account of seborrhœic eczema. Keloids have a very long course, never tend to absorption, and almost invariably recur after excision. Usually, becoming harder and paler, they reach a certain size, where they remain stationary, or develope further, very slowly. The keloids which develope in the course of infectious dermatoses (Eczema, Acne, Furunculosis) usually disappear with their disappearance.

The "hypertrophic scar" is a special form of Keloid, which developes on the base of granulation tissue, and disappears with it. Its relation to the ordinary, traumatic, and also to the so-called spontaneous Keloid, is the same as that of the second to the first intention in scarring, and like that it is a transitory tissue. Keloids due to ulcerative infective processes (Syphilis, Tuberculosis, Leprosy), behave in the same way.

All workers on Keloid agree that the tumour consists of longer-fibred, firm, collagenous tissue, the long axis of which is parallel to the surface of the skin. Inside this fibrous mass, which occupies the centre of the externally visible ridge, the few connective tissue cells are elongated in the direction of the growth, and imbedded in the stiff tissue; the vessels are atrophic or completely absent, the wall-less canals, which are present, appear to be lymph vessels or spaces; hair follicles, coil glands and muscles are also absent, they are found, pushed to a side, above and beneath the growth. The papillary body along with the epithelium is pushed up by the new formation in the cutis, and either flattened out to an a-papillary surface (Babes) or left unchanged (Kaposi).

Mainly on this latter fact, Kaposi has founded a histological distinction between "spontaneous" and scar Keloid, and it is undoubtedly true, that most of the Keloids which develope from scars, indicate this origin by the absence of a well-formed papillary body, and a superficial scar formation, along with the keloid formation. But, as the case of Babes shows, a simple pressure atrophy may also cause the disappearance of the papillary body over "spontaneous" Keloid. Those who value the strict definition between scar Keloid and spontaneous Keloid, and thus a preservation of the latter, set before themselves the task of deciding in every individual case, from the

histological appearances, especially of the neighbourhood of the Keloid, the method of development. They will then find that no single case resembles another, as is not remarkable, in view of the different histories of the development of Keloid. The importance of the process lies, not in the point of origin of the growth, and the accompanying conditions, but in the fact that, in certain individuals, a characteristic fibrous growth succeeds to the most varied trivial traumata, sometimes only transient and very indistinct, which locally extends, like a malignant growth, far beyond the region of the wound, into the healthy tissue, and lasts far longer than the irritant which caused it. Therefore we have to assume in Keloid, as in Urticaria factitia, an individual histological predisposition of the cutaneous vessels. But, as in the latter, the nature of the irritant is not irrelevant, it must be suitable to the skin; we owe an instructive instance of this to Welander, who, in one and the same tattooed figure, found Keloid developed only where the part was tattooed with red, and not where it was tattooed with blue.

Passing from this general view, according to which all forms of Keloid belong to a definite class of growths, it will be our duty to discover wherein consists the peculiarity of keloid tissue, in comparison with other Fibromata of the skin. From the simple Fibromata of the skin, Keloid is distinguished by its elevation over the surface, its smooth character, its sharp margining in one diameter, and its worm-like processes in the other; further, persistent Keloid is distinguished from the hypertrophic scar and other transitory keloids, by its independent extension, its long persistence, and its tendency to recurrence after removal. If histology can explain these clinical peculiarities, we shall be in a position to supply the wished-for anatomical definition of Keloid.

A number of these characteristics have been attributed by several investigators to the fact, that the sclerotic character of the cutis followed the course of the blood vessels. The older Warren found the blood vessels, for some distance around the Keloid, altered and surrounded by cells. Crocker, who has especially investigated the earlier stage, also found the tumour surrounded by numerous dilated and cellular vessels, and though he regards the cells as leucocytes, this only corresponds to the period and methods of examination, without binding us to the view. Crocker further observed a great collection of cells around the follicles and coil glands, and in the neighbourhood, found the epidermis hypertrophic and the ridge system thickened, while over the tumour it was flattened out. The Keloid reached exactly to the papillary body, which also contained numerous dilated blood vessels, in a fine meshed, collagenous net-work, whose fibres, in contrast to the horizontal layers of the tumour, ran vertically.

The (5) Keloids before me are all old, but they also show, around the tumours, in the normal cutis tissue, dilated blood vessels, with abnormally cellular walls. But more important appears to me a discovery, which I recently made as to the nature of the scissor-like root of the Keloid. In a leper, who was covered with 173 recent Keloids, which had formed after the cauterisation of discrete neuroleprides, I extirpated from the arm * a typical, scissor-shaped one, $\frac{1}{2}$ centimetre high, with two pointed processes sinking into the level of the skin. Each process contained a blood vessel as its axis, around which the still cellular, parallel collagenous bundles were arranged. It thus seems to me exceedingly probable, that the pointed roots of Keloid correspond to extensions downwards along the larger blood vessels. It would thus be very simply explained, why most Keloids do not develope equally in all directions; their bodies are usually elongated, and they send their pointed processes from the long ends, where they gradually lose themselves in the depth of the skin, while in the other direction they are little extended, more swollen and abrupt.

But if Keloid is mainly a perivascular fibroma, with its fibres arranged parallel to the vessel, it can only be in a definite part of the circulation that the disease occurs, viz., the branches coming from the lower to the upper vascular net. For the upper vascular net itself, and the papillary capillaries, while they show a multiplication of their perithelia and a dilatation of the lumen, show no adventitial formation of Fibroma; the papillary body does not share in the tumour formation; clinically, we can move it over the Keloid, and pinch it up in fine folds. On the other hand, the Keloid formation does not extend to the subcutaneous tissue; neither clinically nor anatomically do we find fibrous cords extending downwards, which would correspond to the larger subcutaneous vessels. In most parts of the body—on account of the lines of tension—the vessels, which come together from the neighbouring circulation to supply a definite point, are all in a definite, uniform direction, and thus the small ridge-like form of the Keloid is explained by the course of the cutaneous vessels, and the smooth, shining surface by the fact that the papillary body is not affected, and its vessels do not therefore appear as protuberances, but papillary body and epidermis are, as a whole, thinned and stretched.

While, therefore, the form of this Fibroma, in contrast to Fibroma simplex, may be fairly explained by this strict limitation to the vessels of the cutis proper, the characteristic, round swelling and marked elevation over the surface, the cushion form of the Keloid, require further explanation. This, the older, harder Keloids supply. In them, the cellularity of the new tissue has given place to an almost complete

* This contained, as a complication, clumps of bacilli along the vessels.

absence of cells, the blood vessels are reduced to small, scarcely visible, cellular cords, and are often quite unrecognisable. The collagenous tissue, closely arranged, fills the tumour, and shows almost no lymphatic spaces and no elastic fibres. On cross section, we get transverse or short oblique sections of very thick collagenous bundles, which are round, oval, or represent segments of a hollow cylinder, partly surrounding circular segments of other bundles. On longitudinal section, we see the bundles mainly as long or long oblique sections, arranged in parallel over and alongside each other, or crossing at acute angles. The mass of these thick bundles is usually enclosed on all sides by a thin layer of circularly-arranged bundles, which are pushed to a side, and represent compressed layers of normal skin. Then follows, outside, an almost normal cutaneous tissue, in which there is no multiplication of cells, as in the younger Keloids. The Keloid has become encapsuled, having compressed the surroundings, which, like a capsule, restrain its further extension. Thus the increasing pressure has compressed the collagenous bundles still more, into a uniform, parallel-fibred tumour, and made its outward form regularly round. All the connective tissue has passed into keloid tissue, and now the new formation lies like a foreign body in the centre of the cutis, apparently not connected with the rest of the skin.

This striking secondary increase in volume of the Keloid is not induced, like the first formation, by multiplication of the spindle cells, but by interstitial thickening of the already present collagenous bundles. In favour of this is not only the unusual thickness and absence of spaces, but also the striking absence of spindle cells seated on the collagen. In place of a cellular, succulent interstitial tissue, there appears one poor in cells, and finally an a-cellular dry tissue, always becoming harder and more tendinous.

This secondary hypertrophy of the collagenous tissue, shown by the solid swelling and thickening of all the fibrillary bundles, with disappearance of all the other constituents (lymph spaces, cells, vessels), alone induces the appearances of compression described. It also causes the marked elevation of the Keloid over the surface, and thus distinguishes it from simple Fibroma.

The histological definition is consequently the following : a Fibroma limited to the cutis, perivascular in its arrangement, running mostly parallel to the vessels and springing from them, growing later, with atrophy of the vessels and cells, into a pure collagenous, uniform structure, compressing the other constituents of the skin.

The transitory Keloid, which developes on the base of granulations or infective granulomata (Lupus, Syphilis) and other infectious inflammations (Acne), is distinguished from the persistent one, mainly by the

fact, that the liability of the vascular adventitia to fibromatosis is only transient. Thus these Keloids never reach the last stage of pure collagenous hypertrophy, from which there is no recovery; they are not encapsuled, their lymph spaces are not destroyed, and their cells and vessels do not completely atrophy. Thus complete restitution is possible by simple absorption of the fibrous mass; we have once more a simple scar, a simple syphilide, and so on. If such a hypertrophic scar is removed, there is a possibility that no new Keloid will appear in the new scar, for there is no tendency to fibromatosis. We also find that the keloid scar never extends, with fibrous processes, into the healthy tissue, for, being due to the granulation, it is only present in its neighbourhood. But apart from these differences, which are founded less in the act than in the condition, transitory Keloid is in no way distinguished from the first stage of persistent Keloid.

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(β). *Neurofibroma.*

Neurofibromata always appear multiple, they are rarely regionally limited, usually universal, and then very frequently accompanied by plexiform Neuromata of the cutaneous nerves and the nerve trunks. The nodes at first lie at the under margin of the cutis, and small, movable processes may be recognised extending downwards. As they grow, they unite with the skin, elevate it into round projections, and finally form tumours, the size of peas, cherries, or apples, usually with a broad base, which hang down by their weight, and draw after them broad folds of the skin, but have no tendency, like the nævi, to be pedunculated. In these larger tumours, we can feel a lobulated, or rather plexiform formation, for the individual cords may be moved on one another. The Neurofibromata are distinguished from the Fibromata of the skin, by their softness and their transparent tissue. The smaller nodules, projecting over the skin, are yellowish and transparent, the larger ones, bluish-red. A further distinction from the fibromata of the skin is their mobility, so long as they are still small, and even afterwards, their invariably recognisable connection with movable cords (bundles of nerves) under the skin. Occasionally they appear

alone, but are often accompanied by other forms of congenital tumours (nævi, pigmented moles, angiomata, pachydermatocele, and other forms of congenital elephantiasis).

It is to the everlasting credit of v. Recklinghausen, that he has, by a thorough clinical and most careful anatomical investigation of the Neurofibromata, once and for all separated this class of tumours from the cutaneous Fibromata, and thus made a commencement of order in that group of tumours, which, under the names multiple fibromata, fibromata mollusca, and the different forms of congenital elephantiasis, were a completely unarranged and obscure congeries. The Neurofibromata are, as the name indicates, no proper cutaneous Fibromata. They are formed of another sort of connective substance than the cutis, are soft and transparent, and evidently developed by the ingrowth of this new connecting substance from beneath into the skin, whereby the greater part of the cutis—but not all—is gradually replaced by this soft, neuromatous connective substance. This is familiar in the plexiform Neuroma, and corresponds exactly to the hypertrophic tissue of the inner lamellar sheaths of the nerve cords, in the formation of these nerve tumours. It grows, as v. Recklinghausen very exactly describes, from the subcutaneous nerve trunks into the skin, surrounds, first the deeper-lying organs, *supplied by nerves*, the coil glands, then, extending along the nerves of the skin, the blood vessels, muscles, follicles, and, dividing into finer bundles, runs towards the epidermis. This cord-like ingrowth explains fully the initial mobility and the later greater fixation of the nodules in the skin, as well as their composition from somewhat movable cords, and the possibility of tracing these into more isolated and movable subcutaneous ones.

After v. Recklinghausen, Kriege very carefully investigated the relations of the cutaneous nerves and the cutaneous tissue in the formation of Neurofibroma, and, after examining three cases of my own, I can fully confirm his statements. The subcutaneous nodules show a distinct plexiform arrangement. They consist of cords of finely fibrillated, transparent, cellular connective tissue, which are held together by ordinary, loose connective tissue. Medullated and non-medullated nerve fibres run through it, rarely united, usually widely separated from each other. In finer sections, we can still recognise the outer dense layer of the nerve sheath, which, by the growth of the inner layers, is enormously dilated. Since this, normally, gradually disappears in the cutis, it is not remarkable, that in the cutis the proliferating peri- and endoneurium show hardly any membranous margining. Nevertheless, the border of the tumour is everywhere sharp, both macroscopically and microscopically, because the form of

connective substance is completely different from that of the cutis. If the individual nerves of a nerve bundle, entering the skin, are separated by the growth, this is still more striking in the organs of the skin which are supplied by nerves. The coils are either completely pressed outwards, or, by the development of neurofibrous tissue between the loops, unrolled. Hair follicles are sometimes constricted between sebaceous gland and papilla; the lobules of the sebaceous gland are separated from one another; the normally elongated ducts of the coil glands, the muscles and even the blood vessels, are still more stretched and elongated. It appears as if all the organs of the skin were mechanically affected by the development between them of the tumour, without suffering in nutrition. No doubt, the more the mass of the tumour increases, the more is the normal connective tissue of the coil glands, the hair follicles and the vascular sheaths lost, and replaced by transparent neuro-fibrous tissue. Thus, in the larger nodules, the organs of the skin come to lie naked in it, like the nerve fibres themselves. But the epithelial elements only suffer mechanically. There are even found, in some coil glands, signs of proliferation of the epithelia, and in others, true adenomatous growths. Others again are occasionally bent and narrowed by stretching, and there result partial dilatations of the lumen, with stagnating, yellowish, hyalin contents. There often correspond to a subcutaneous Neurofibroma, several discrete nodules in the cutis. Usually, the more fully developed main nodule is surrounded by smaller supplementary nodules, which gradually assume the character of the pure Neurofibroma. Especially in these latter, can one, even in the cutis, study the plexiform basis of the tumour, due to the development from the nerves, since it sends individual cords to the individual organs of the skin. Here, one also recognises remains of the outer, denser layer of the perineurium, and it may be that cords, at once recognised by their being covered with this sheath, are found in the free growing tissue of the principal nodule. These are the smaller nodules, not completely united with the cutaneous tissue, which are microscopically evident as isolated cords, and may sometimes be clinically recognised by touch.

The epidermis is very rarely reached by Neurofibroma. Usually the papillary body is unaffected. Where the tumour is more fully developed, the epidermis, with the papillary body, is distended and stretched. In true Neurofibroma, there are no degenerations of the epithelium and the epithelial appendages. The regular cystic degenerations of the hair follicles in the centre of the tumour, described by some authors, show, on other grounds, that the tumours were not Neurofibromata, but polypoid nævi or some other form of Fibroma. (Hilton Fagge, Lahmann). The epithelial growths, described by

others in Neurofibromata, may also be caused by a local complication with nævus formation, and one cannot be too careful to avoid including the thoroughly distinct type of nævi along with the Neurofibromata. For thus the great advance inaugurated by v. Recklinghausen would be lost.

The nerve fibres, as v. Recklinghausen and Kriege have recognised, are thus neither increased nor diminished in the Neurofibroma. They are as a whole unchanged, and only pressed asunder, and though their calibre is now and again diminished, their number may appear increased. While they are only met singly in the upper parts of the larger tumours, we frequently find, in the small, invisible nodules, partly as spirally winding longitudinal sections, partly as Mitrailleuse-like cross sections, a well-preserved neurofibroma branch; similar appearances are found in the central sections, at the base of the large nodules, at the margin between cutis and hypoderm.

The blood and lymph vessels, which penetrate the nodule, are, in general, distinctly wider than normal; even the lymph spaces between the individual cords are wide and gaping. But since the hypoderm is not affected by the new formation, and the subcutaneous arteries retain their normal muscular sheaths, there is no great amount of blood in the tumour during life. There is no emigration of leucocytes from the vessels.

The neuro-fibrous connective tissue in the larger nodules, where the original cord-like character is completely lost by the introduction of a regular new formation between the cords, is a regular, yellowish-grey, transparent mass, and, in sections with transmitted light, very sharply defined from the rest of the cutis. It usually forms a typical cone, whose blunt apex is found around a coil at the subcutis margin, while the globularly rounded base reaches close to the sub-epithelial marginal layer. With a hæmatoxylin-orcein (acid) stain, these cones stand out blue from the orcein red ground, for the new formation—like the peri- and endoneurium—is completely free from elastic tissue. With an orcein-methyl-blue (neutral) stain, they take a bluish-grey colour, and reject the orcein stain of the rest of the collagenous tissue.

In general, the inter-cellular substance of the Neurofibroma is difficult to stain. It is not distinctly fibrillary, like the collagenous tissue of the cutis, but very irregularly formed, and difficult to describe. It is a spongy, ill-defined, glassy substance, penetrated by many spaces, which only shows, along the enclosed organs, where the cord-like character is evident, a sort of division into regular, long fibres. The cavities are, a few of them, empty, and represent lymph

spaces; most of them are occupied by equally large cells, one may almost say nuclei. For the body of these cells is much more difficult to demonstrate, than in the surrounding collagenous tissue. Where this is successfully done, by a good methyl-blue stain, we see a fine glassy, non-granular rim, which surrounds the large, always oval or spindle-shaped nucleus. The nuclei of the neurofibrous tissue are much more numerous than those of the surrounding tissue, more approaching in number those of a Fibro-sarcoma. The nuclei lie separated by rafters of spongy, inter-cellular substance, and are very regularly distributed, similarly to, though in greater numbers than in normal endoneurium.

The most striking constituent of the Neurofibroma is the mast cell and a peculiar variety of it. (Front., Fig. 16.) These, also, are pretty regularly distributed over the new formation. In the larger nodules, they are present in quantity, and in greater abundance than in the surrounding cutis, where they only accompany the vessels in somewhat increased numbers. In the smaller nodules, they are less numerous in the nodule, but pretty abundant in the immediate neighbourhood. We see first, ordinary mast cells, which, stained with polychromic methyl-blue, show, in addition to a small blue nucleus, the deep red granules collected in a regular, dense, oval halo. But, even with a low power, we see in some nodules, in addition to a few ordinary mast cells, others surrounded by a large, red halo, about double the size of an ordinary mast cell. This halo shows the same red colour as the granules, but, as a high power shows, is not granular but very finely spongy. It is therefore a spongioplasm, peculiar to the mast cells, staining like the granules. A thorough investigation of these cells shows, that they surround the central nucleus a-symmetrically. Usually one finds, only on focussing, a shell of red spongioplasm, and in this open shell lies the nucleus with its granules. Sometimes processes of the spongioplasm extend around this latter structure, and meet on both sides, so that it is partially but not completely covered by a mantle. In other cases, the red halo only has the form of an irregular plate, giving off thready processes in different directions, and which only lies alongside the mast cell, if we restrict the term to the nucleus and granules—the cells thus recall the winged cells of tendons. In other cases, again, we see a bell or jelly-fish-shaped spongy mass, with veil-like processes, in whose cavities the nucleus and its granules lie.

Evidently, we are dealing with a very widespread mucous change of the connective tissue cells, which is quite peculiar to the Neurofibroma, and must be borne in mind in the diagnosis of this tumour.

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(b). *Neuroma.*

After the removal of the Neurofibromata and the plexiform Neuromata from the Neuromata proper, there remain only very few, which, according to Virchow, are to be described as *terminal neuromata.* They are distinct, generally small tumours, which usually develope after an injury during incision, only rarely spontaneously, or are amputation-neuromata of nerve trunks, which have become adherent to the scar.

Axel Key observed a soft, encapsuled, rapidly growing tumour, the size of a plum, on the nose of a man of thirty-one. On section, it was greyish red, like a sarcoma. There were groups of two or three ganglia in it, which were connected with the nerve fibres. This was then the rare occurrence of a cellular Neuroma of the skin.

Virchow notes a series of cases of terminal, partly myelin, partly a-myelin neuromata, of traumatic origin, from Weismann, Grainger, Adams, Reich and others, of which only that of Weismann is beyond suspicion.

> Weismann had himself been cut by a piece of glass on the volar side of the thumb, a branch of the median being divided; the wound did not heal, and a part of the nerve had to be removed. In the course of a year and half there formed, in the painful scar, a small tumour, which was very tender, and finally was extirpated. It consisted of medullated nerves.

The case of Verneuil, also noted by Virchow, was etiologically a

Neuroma, but from its anatomical structure certainly a Neuro-fibroma.

The patient was a man, forty-one years of age. Four years previously, there formed an inflammatory, very tender swelling of the prepuce, which gave rise to severe nervous disturbance, with spermatorrhœa and general debility. It was for a time regarded as chronic Herpes preputialis. It consisted mainly of thickenings of the terminals of the cutaneous nerves. In addition to large thick veins, there was found at the border of the prepuce a sort of ring-formed nerve plexus, from which the thickened nerves ran in all directions to the surface of the skin. Many of them were a third, a half or even more thickened. The thickening was mainly in the sheath of the primitive fibres, some of which were well preserved, while others were atrophic. The inter-tissue had shared in the thickening.

The relations of the rest of the skin to the Neuroma, and the development of the latter from the cutaneous nerves, appear not to have been thoroughly enough examined. Probably there were, as in the "Tubercula dolorosa" of the hypoderm to be immediately described, in these cases, different conditions, true and false neuromata of the cutis, and the growths were only extirpated and available to us, and only resembled each other, because the particular form of nerve distribution induced a tension of the nerve fibres, and thus hyperæsthesia. For the extraordinary rarity of these growths is quite remarkable, considering the frequency of wounds of the nerves. We must also recollect that all Neuromata are by no means painful, and that many cases of Neuroma of the skin escape us, because they are embedded in soft, yielding tissue. The largest racemose-neuromata of the subcutaneous tissue are notoriously as little painful as the soft Neurofibromata.

We have the same experience in the distending or amputation-neuromata, which sometimes are insensitive to prolonged squeezing, while others cannot stand the prolonged pressure. Here also we are as yet unfamiliar with the anatomical details of the change. Over these painful Neuromata, the skin is usually swollen and sensitive. "Continuity" Neuromata, when fully developed, may also secondarily affect the skin, as the case of Blasius (Virchow) shows.

The thorough investigation of these cutaneous Neuromata demands not only the application of osmium, but also of the gold method, for non-medullated fibres may be affected.

Somewhat better known, and more frequently examined, are the true and false *Neuromata of the hypoderm*, the so-called Tubercula dolorosa.

Since Wood (1812) described a form of tumour, under the name "painful subcutaneous tubercle," a considerable amount of literature has accumulated,

without any uniform view as to the nature of the change. They usually form small, pea-shaped nodules, which are seated in the subcutaneous tissue between cutis and fascia, usually on the forearms, hands and legs, especially in the neighbourhood of the joints, and are painful, either spontaneously, or on the slightest pressure. Usually they are single, rarely multiple, always appearing in adults, especially nervous women. Some authors have therefore assumed that the tenderness lay, not in the nature of the growth, but in the irritability of the patient (Broca, Paget). But against this is the fact, that where they are multiple, only some are painful, that the pains are neuralgic, and may be produced at will by pressure.

Anatomical investigation has proved that the tumours may show quite different structures. Broca, Paget, Vallender, and Follin described simple Fibroma; Chandelux—Fibro-myxoma; Bégin and Sanson—Lipoma; Busch and Müller—Enchondroma; Billroth—Leiomyoma; v. Baerensprung, Schuh, Monod, Trélat—Angioma; Windsor and Broca—Sebaceous cysts; Hoggan and Chandelux—Spiradenoma;—all causing the same clinical symptoms. True Neuromata were recognised in some cases by Velpeau, Axmann, Virchow, Labbé and Legros, and Chandelux. But since Labbé and Legros, using the osmium and gold methods, found nerve fibres in the painful nerve tumour or on its surface, these have never been missed. We have therefore now to distinguish two main forms of Tuberculum dolorosum: (1) *true Neuromata*, and (2) *any kind of subcutaneous tumour containing nerves.* It is tempting to attribute to these gross anatomical differences, the clinical variance in the amount of tenderness, and to regard the spontaneously painful tubercula as Neuromata, those which are only painful on pressure as some other nerve-containing tumour. Chandelux has made another division by ascribing the periodical critical pains to a turgescence of the blood vessels in some nodules, the inducible pains to the exposed position of the nerves, which usually lie superficially on the nodules, in their furrows, or between phalanx and nail. Whichever it be, it is the duty of histological investigation in future cases, to find the factor which distinguishes the nerves of these new formations, be it their course or their position in the tumour, from the nerves of other similar growths. For the simple existence of the nerves in them no more explains the tenderness, than the general nervousness.

As Chandelux notes, we can only speak of a neuromatous nature of the tubercula, where there is a great number of newly-formed nerve fibres, and a want of relation between the mass they form and the nodule. Neuromata which are only to be felt through the skin, but do not lie above the fascia, are not Tubercula dolorosa. The true Neuromata among the Tubercula dolorosa, are best described, according to Craigie and Virchow, as "neuromations."

Virchow has described such a "neuromation," the size of a bean, from the ankle, which consisted almost exclusively of non-medullated nerve fibres. Labbé and Legros also found an abundant felting of nerves, partly with, partly without angiomatous change of the vessels. Chandelux describes a subungual "neuromation," in which a Pacinian corpuscle, along with numerous medullary nerves, was found between the fat lobules and the blood vessels. Axmann had already demonstrated a Pacinian corpuscle in a nodule from the elbow. Labbé and Legros finally described a case with papillary excrescences, each one of which contained a touch corpuscle.

The Tubercula dolorosa of non-neuromatic nature have been studied by Monod, Hoggan, and especially Chandelux, in regard to the behaviour of the nerves. It appears to me, that histological investigation has to discover, in all these cases, something mechanical, which gives origin to an abnormal tension of the tissue, in which the nerves expand. For the clinical peculiarity of these tumours lies mainly in the fact, that slight traumata induce severe pain. Thus the above authors frequently find the nerves distributed on the tense capsule of the tumour. The important histological quality of a subcutaneous nodule, which makes it a "tuberculum dolorosum," must be sought in the fact, that the tumour is firmly enclosed by collagenous tissue, and, at some point of greater tension, encloses sensory nerve twigs.

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(c). *Angioma.*

As will be seen under the congenital tumours of the vessels, I separate the vascular moles, both the flat and the elevated, completely, from the Angiomata proper, because they represent, histologically and

clinically, a type of their own. Histologically they are primary angiectases, without any capillary budding. Most modern text-books do not sufficiently separate the vascular moles from the true Angiomata of the skin, no doubt mainly because the latter are also congenital. Nevertheless their main development is in extra-uterine life, while the angiomatous nævi are distinguished by their remaining stationary. Whether they may pass into true Angiomata is still in question; literature is not of much assistance, for, with the exception of Virchow, most authors do not sufficiently distinguish Venous nævi from Angiomata.

After separation of the vascular moles and all the other Angiectases, it is no simple group of tumours that remains. There can be no doubt as to the nature of that form which Virchow describes as *Angioma simplex hyperplasticum*, and Winiwarter as *Angioma plexiforme;* it is a pure "rodent" (Virchow) structure, spreading by capillary budding. As it represents the most common type of Angioma of the skin, it may be described, as the typical cutaneous angioma, simply as Angioma. It may, as we shall see, in places become varicose, and even cavernous, without losing its own character.

But matters are different in the so-called *Cavernous angiomata* of the hypoderm, which, in spite of Virchow's classical discussion in his work on Tumours, are still shrouded in darkness. The old view of Rokitansky, which Virchow opposed, that this form is originally a connective tissue growth, which contains lymph and not blood in its meshes, has received an important confirmation by the recent investigations on the hæmangiomatous transformation of Lymphangioma (which see). Winiwarter describes others of them as independent growths, analogous to the Corpora cavernosa, and finally Virchow's view of the development of the Cavernous angiomata by the gradual erosion and rupture of the vessel walls of an Angioma simplex, holds for some, especially the encapsuled angiomata. So far as these develope from lymphangiomata, I shall consider them with these tumours; so far as they are results of simple angiomata, they deserve no special title. So there remains only the form described by Winiwarter as analogous to the Corpora cavernosa, and—since I have no personal experience—I will take the description of the primary cavernous angioma from this author, in the expectation that his view will be confirmed.

The "phlebogenous" angiomata of Esmarch, which are now and again found in numbers on the venous trunks of old people, are, according to Virchow, true angiomata of the vasa vasorum; we need hardly consider them; they have little connection with the skin. Thus we have only two forms to consider—*Angioma simplex* and *Angioma cavernosum*, of which the former is by far the more frequent and important.

Angioma Simplex s. glomeruliforme.

The *simple Angioma* forms a tumour, the size of a cherry-stone to a walnut, or larger, at first smooth, later often irregularly lumpy and swollen, soft and compressible, which commences in the substance of the cutis, especially at the subcutaneous margin, and grows sometimes towards the epidermis, sometimes towards the hypoderm. The tumours are always macroscopically well defined. It is not possible to divide them into cutaneous and subcutaneous. The deep ones are dark bluish black, the superficial ones bluish red. Like all Angiomata, they swell from the action of gravity and of abdominal pressure, but only the largest ones, and especially those over bone or cartilage, pulsate. With the diascope they show only points and drops of blood, and no long lines, like the vascular moles. Like these they are mostly congenital, but develope first in extra-uterine life, and then often in an unlimited manner, which clearly distinguishes them from angiomatous nævi. Usually they are seated singly on the head or neck, more rarely on the trunk and extremities. Now and again there is spontaneous regression or cystic formation, more frequently a partial cavernous change.

The simple Angioma consists, as Virchow has clearly described, of a convolution of winding, hyperplastic capillaries, which end on one side in arteries with very cellular and muscular walls, on the other in dilated veins; it is consequently the arterial capillaries of the skin which form most of the angioma, while in the vascular mole (which see) the venous capillaries are mainly affected. As the venous capillaries there, show not only dilatation of the lumen, but abnormal conditions of the walls, here, the arterial capillaries are not normal. Only the youngest buds, coming from healthy tissue, consist—as usual—of protoplasmic spindle cells, which show double their ordinary length, and between them, a fine canal which communicates with the nearest blood capillary. But in these pointed capillary buds, the thickness and firmness of the endothelium and the gaping of the walls is remarkable. In the tumour itself the endothelium is usually in two rows, more protoplasmic than normal, and even arranged concentrically in several rows, so that the lumina—in marked contrast to the normal capillaries—gape.

In addition to the budding, by which the still healthy skin and fatty tissue is invaded, atrophied and substituted by new capillaries, one can distinguish, in growing Angiomata, an interstitial capillary enlargement, indicated by numerous mitoses in the endothelia of the already formed capillaries. This leads to enlargement, elongation, and, from the limited space, to greater winding of the capillaries, and thus to compression and condensation of the cutaneous tissue above. The more the external capillary budding predominates, the more rapidly does the Angioma extend in all directions; the more the in-

terstitial endothelial proliferation, the more does the tumour tend to encapsulation, and to remain stationary. The majority of the specimens before me—pure cutaneous (two), pure subcutaneous (two) and mixed (three cases) angioma—shows the last type. To this multiple looping in a limited space, as well as to the pressure of the adjacent tissue, is due the frequently-noted tendency of the tumour to lobulation. Every segment of skin abundantly supplied by capillaries, forms its own vascular coil, and the relation of the lobules to different organs of the skin, noted by Billroth, as explaining the formation, is to a certain extent justified. But there are also fully formed lobules, consisting of vascular coils, without any relation to the hair follicles and coil glands, *e.g.*, on the surface of the skin; and, on the other hand, we may very frequently observe a radial budding in the neighbourhood of the coil glands and inside the fat lobules, where the main seat of the angiomatous lobules should be. Only when such a fat lobule is permeated by vascular buds, which are arrested by the adjacent firm connective tissue septa, and the capillary loops are arranged in denser and denser folds and loops, does there result, here also, typical lobule formation. The coil formation and the subsequent lobulation of the whole Angioma are therefore not limited to the immediate surroundings of the follicles and glands, but develope everywhere where the interstitial growth predominates, and the advancing capillary budding meets any hindrance. Thus we see that, while the firm cutaneous texture, in general, favours the coil and lobule form of the angioma, and the subcutaneous tissue does not, the complete angioma of the fatty tissue shows the most typical lobulation.

This coil formation so distinguishes the Angiomata of the skin, developed from arterial capillaries, and forms such a marked distinction to the nævus, formed of venous capillaries, that, were the adjective simplex not sufficient, we might use in the same sense the words *arterial* and *glomeruliform* for this most frequent form of Angioma. At least these adjectives appear to me more suitable than that used by Winiwarter: *plexiform*. For all the capillaries of healthy as well as of diseased skin form plexus, and the contrast to the formation of nævus is not made so clear.

The elastin disappears much more in Angioma than in nævus. From where the arteries pass into the hyperplastic capillaries, there is not a trace of elastic tissue, and, in the after increase of the capillaries and thickening of their walls, it does not again develope; the complete Angioma is an entirely inelastic tumour. Since there is no elastic or muscular marginal lamella, the thickness of the walls of the capillaries is difficult to estimate. The endo- and perithelia are only grouped concentrically around the lumina of the capillaries, and the margin of

the vessels is to be placed where the perithelia of different capillaries are adjacent. In less dense vascular loops, the capillaries look just like canals, excavated in an equally cellular connective tissue, and the more, as this inter-tissue gradually loses the structure of the cutaneous tissue, shows no elastin, becomes less fibrillary and more homogeneous, and, in the orcein methyl-blue method, instead of the orcein, takes up the methyl-blue.

The venous capillaries are simply dilated, and may be recognised in the Angioma, as relatively stretched, wide tubes, clothed with simple endothelium.

The influence of the growing Angioma on the enclosed organs of the skin is evident in different ways. The ridge net of the epithelium is shortened under the pressure of the cutaneous Angioma, and disappears, the whole prickle layer is thinned; the hair follicles also are shortened, and atrophy. On these epidermic structures, pure subcutaneous Angiomata have no notable influence. But it is otherwise with the coil glands, which are seriously, and apparently early affected in all angiomata. We often find, in the still healthy surroundings of the Angioma, the capillary net of the coil glands showing proliferation. The whole gland is very soon surrounded by a vascular coil, and, as the growth extends, is unrolled, so that the individual loops of the gland are evident, widely separated, inside the vascular coil. In the glandular epithelium, except for an enlargement of the cells, we note no change; the epithelium of the duct tends to be increased, and shows three or four layers and a very thick cuticle. In the central, larger loops of larger Angiomata, there are still further changes; the volume of the glandular epithelia diminishes, the lumina disappear, the whole gland shrinks and becomes unrecognisable. I have only once observed the opposite, a growth of the coil epithelia, which had led to an irregular form and adenomatous protuberances of the gland. Certainly in this case it was not difficult, by means of staining, to distinguish the epithelia and the endothelia from one another, and in the lobules of the Angioma, containing coil glands, a differentiation of glands and vessels is always easy, for, in addition to the different stain, the close and regular arrangement, and the larger, more regular form distinguish the glandular epithelia. But in the earlier days of staining, this distinction may have been much more difficult, for Virchow regarded Lotzbeck's case of Adenoma of the sweat glands, as an Angioma.

The muscles and nerves are embedded in the Angioma, without showing any particular changes. In some cases, an increase of the smooth muscles of the inter-tissue may be observed, but I have not found it in my preparations. There is no new formation of muscle in

the vessels. Virchow inclines to attribute the contractility of many Angiomata to the musculature of the skin. I believe, that in this very rarely recognised peculiarity, which is sometimes accompanied by spontaneous tenderness, the traction of the large, supplying arteries, which must induce a marked diminution of the tumour, comes into consideration; in this I do not include the combination of Angioma with Myoma of the skin, which shows true contractility.

As a last, unimportant, but apparently constant constituent of the angioma, we must note the mast cells, which, though not numerous, are very large. They are usually distributed in the inter-lobular connective tissue, but are also found in the middle of the lobules of the Angioma. Very often they are surrounded by a zone of free mast cell granules, or of diffuse mast cell stain.

In all the longer existing and larger Angiomata, we find in places a tendency to varicose and cavernous form, without the glomeruliform main character of the tumour being lost. For the altered vessels join directly the greatly dilated veins, and one may therefore regard the varicosity of the Angioma simply as a shortening of the arterial capillaries, in favour of the venous. This change takes place in two different ways; either by simple dilatation, or by a concentric breaking down, an erosion of the endothelium of the hyperplastic capillaries.

The first method is almost typical of the upper papillary part of the growth, and I imagine that the confusion of angioma with the very different angiectases of the papillary body, is due to this appearance. With the enlargement of the whole Angioma, the diameter of the arteries leading to it also increases, and the blood pressure is greater, and it is only natural that wherever the tissue pressure is less and the yielding of the tissue greater, dilation should exceed endothelial growth. Then, with dilatation of the lumen, the endothelia separate, the numerous layers give place to a single one, and finally the nuclei of the endothelia are so separated, that the ordinary type of venous endothelium is attained. This formation of varix takes place in many places near the surface, and may form a complete cap over the glomeruliform growth in the cutis and hypoderm. After the papillary body, another seat of predilection is the loose connective tissue septa which run through the Angioma, and mostly extend along the large veins. Where a few larger follicles persist, varicose distensions readily take place into the loose connective tissue around them.

I found quite another method of vascular dilatation in two of my preparations. Here, there were a number of hyperplastic capillaries in the centre of the growth, blocked by endothelial giant cells, with numerous nuclei and a peculiarly perforated protoplasm. In other capillaries, very large protoplasmic endothelia extended across the

lumen, while others only had part of their protoplasm separated from the walls. Still others showed an almost complete ring-formed separation of an internal, endothelial layer, which projected, folded, into the lumen, and finally, some capillaries were completely free from these loose endothelia, and showed a very large lumen and a peculiar, irregular, nibbled endothelial lining. There are, therefore, two stages of the whole process, the first of hyperplasia, with swelling of the endothelia, formation of giant cells, and solution of their connection; and the second, which may be shortly described as endothelial "scaling." Thus, in the densest part of the growth, which certainly did not incline to dilatation of the capillaries, comparatively rapidly formed varicose capillaries developed; indeed, some neighbouring capillaries ran together to form large, irregular cavities. I am inclined to explain in this way the larger blood spaces, occasionally found in the centre of larger, glomeruliform Angiomata, for, in the first place, there is a greater tissue pressure, and thus no opportunity for dilatation, and secondly, because the already dilated vessels of the papillary body in these Angiomata show no tendency to cavernous coalescence, as do the varices in Angiectases and nævi of the papillary body. And the formation of larger blood vessels inside Angiomata, which have been snared off from the rest of the new growth, and are sometimes found filled with hyalin degenerated coagula, is most easily explained by this process of endothelial degeneration. That the pure cavernous Angiomata develope in this or some similar way from the glomeruliform (Virchow), has recently been shown to be improbable.

Angioma Cavernosum.

The true, primary cavernous Angiomata are, according to Winiwarter, diffuse or defined, soft tumours, of lobular formation and semi-spherical or protruding surface. Their colour is steely-blue, only rarely red. The encapsuled subcutaneous ones are movable beneath the skin. On pressure, they diminish the more, the larger are the blood spaces. They readily become turgescent even on compression of the neighbourhood. They are frequently very painful. They are more rarely congenital than the simple angiomata, and usually appear in the first year of life, sometimes owing to a trauma, especially a pinch. They are usually subcutaneous and solitary, more rarely cutaneous and multiple; they are more common on the extremities than the simple angiomata. Their growth is slow, but sometimes they extend, uninterruptedly, to the mucous membranes and the eye, attacking soft tissues, and destroying bone and cartilage. Sometimes they are transformed into non-compressible blood cysts.

Macroscopically, the cavernous angiomata are, on section, diffuse or encapsuled tumours, of fine or coarse pored structure, somewhat collapsing from the loss of blood, which enters and leaves them by a few

large veins. The numerous communicating spaces of the tumour are clothed with flat venous endothelium. In the younger parts we see in their walls numerous new-formed muscular fibres, giant cells and vacuoles. Winiwarter regards the development of these tumours as analogous to that of the Corpora cavernosa penis, since inside the walls of venous vessels, cell growth and giant cell formation appear, and by vacuolation and excavation of solid vascular bodies, instead of ordinary capillaries, broad communicating spaces develope. According to him (in contrast to Virchow), there are true phlebogenous cavernous angiomata, with no arterial supply.

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(d). *Myoma.*

The myomatous tumours of the skin, which contains almost entirely smooth muscles, are all Leiomyomata. The mimic striped muscles of the face, scalp and neck, which enter the skin, never give rise to tumours. Especially disposed are those regions which normally show larger masses of muscle, such as the scrotum, the large labia and the areola.

Virchow first described these tumours, from the areola of a man thirty-two years of age. They had slowly developed, in thirteen years, to the size of a cherry, and were very painful. On account of the simultaneous abundant development of vessels, Virchow named this form, Myoma teleangiectodes. Cases were afterwards described by Klob and Sokolow. Förster, Challard, Valude, Phélisses and Babes communicated cases of Myoma of the scrotum and the labia. In Babes' case there was both congenital elephantiasis and a more diffuse extension of the myoma. The skin, especially on the genitals and under extremities, was folded and warty, deeply pigmented and translucent. At the seat of the warty elevations, the cutis was brawny, poor in cells, and rich in blood and lymph capillaries. Underneath, the deeper part of the cutis was smooth and horizontal, and consisted chiefly of a layer (1 millimetre thick) of muscle fibres (0.3 millimetre thick), each enclosed by its own connective tissue sheath. Babes attributed the folding of the skin to the contraction of the deep Myoma.

Most of the tumours of this form were circumscribed, in one case (Challard) even pedunculated. Many cases are subcutaneous and per-

haps arise from aberrant muscle cells of the skin. Thus Marcano described a myoma of the labium majus, the size of an orange, which was readily shelled out and arose from the aponeurosis beneath.

Where single Myomata develope independently of the large muscle layers of the skin, there is often a complicating nævus, which, in addition to its other characteristics on the surface, shows, deep down, a dense collection of smooth muscular fibres. These tumours may, as Virchow has already noted, also develope from small Angiomata, by excessive development of the vessel muscles. Babes found, in such a Myoma from the subcutis of the palm, inside a fibrous capsule, a dense coil of smooth muscle fibres, in whose individual cords a tiny vascular lumen or a row of endothelium could be observed. Such were possibly the case of Brigidi and Marcacci, in which the small muscular nodules of the hands and feet were embedded in a red-spotted, œdematous skin, and that of Axel Key, which was probably a lymphangiectatic myofibroma.

All these isolated Myomata probably belong to the congenital tumours, and, if carefully examined, would probably supply much of interest, both for the histogenesis of the smooth musculature of the skin, and for the theory of aberrant germs, for the normal seats of smooth muscles (vessels, arrectors, dartos) are known and are widely separated. The latter theory applies especially to the Myomata, for the numerous inflammatory and infectious dermatoses, which are accompanied by a hypertrophy of the oblique muscles, never give origin to myomatous formation in extra-uterine life. That is only occasionally, apart from the circumscribed independent growths, added to other tumours (Fibroma, Angioma, Sarcoma, Xanthoma).

We have only recently become familiar with the *disseminate spread of Myoma*, from Besnier's description, and since then the cases have, through the works of Arnozan and Vaillard, Jadassohn and Lukasiewicz, so increased, that we are able to describe, both clinically and histologically, this form of Myoma.

> In younger, or older people, usually women, there develope, in the thickness of the cutis, firm, red nodules, the size of a mustard seed, which, in the course of years, grow to the size of a lentil, or larger, and project the epidermis over them. The larger, dark coloured ones are always sensitive to pressure or cold, under which they sometimes pale and retract. In some cases there are paroxysmal, spontaneous pains, which make the affection one of torment. They are usually seated on the extensor sides of the extremities, especially the arms, but are also found scattered on the trunk. On the face (nose) they have only once been observed (Hess). The surface of the skin, sensibility and the secretion of sweat, are normal. Except for a slow increase in size and a partial involution, they show no changes.

In all these cases the myomatous new formation lay in the cutis

itself, often filling it from epiderm to hypoderm, while in some cases it was limited to the lower layers (Besnier-Balzer) or to the upper (Jadassohn's second case). Usually, at the perceptible margin of the tumour, it passes gradually into the surrounding cutis, the muscular bundles separating and becoming fewer, as the collagenous tissue penetrates between them. Hess alone describes a sharper limitation of the myomata of the skin of the nose, caused by the fact that the nodules pushed the surrounding parts, hair follicles, coil glands and collagenous tissue, to a side, and in this way became encapsuled. In this case there were also other peculiarities; the centre of the nodule was completely avascular, and the colour was therefore yellowish, not reddish as in all the other cases; the tumour shelled out readily at the operation. Their relation then is something like that of Keloid to diffuse Fibroma; whether this peculiarity is simply connected with the peculiar seat of the nodules, or indicates an especial variety of disseminated Myoma, must be left to further experience.

While Hess thinks that in his case he has definitely determined the origin of the nodule from the muscular coat of the cutaneous vessels, and is not inclined to attribute the avascularity of the centre to a complete passage of the vessel into myomatous substance, Jadassohn found, even clinically, in one of his cases, a lanugo hair follicle in the centre of every Myoma, and confirmed, histologically, the close relation and connection of the muscular bundles with those of the hair follicles. Lukasiewicz also found a connection between the tumour and the muscles of the hair follicle, and noted that at the seat of the follicles they reached nearer the surface; but he also determined a direct transition of the myoma spindles into the vessel musculature, and further into the muscles of the coils. The older authors are less clear on the point of development of the tumour cells.

While then the point of origin is still uncertain, and perhaps varies, the form of the growth described by all authors is the same; a dense net of muscle fibres crossing in all directions, most compact in the centre, looser at the periphery, and here permitting the entrance of blood vessels. It is permeated inside by an abundant net of elastic fibres, nerves are found at the periphery, but sparingly, or not at all, inside. Arnozan, Vaillard, and Lukasiewicz found a moderate infiltration with "round cells" around the vessels, but do not more closely indicate their character. Lukasiewicz regards them as a sign of inflammation. Jadassohn found them also; he noted that they did not possess fragmented nuclei (are therefore not leucocytes), and he lays stress on this. The cellular areas occupied, in his first case, mainly the papillary body, and then the surroundings of the sebaceous glands and coils, which latter were almost completely obliterated and un-

recognisable. He also would regard them as the sign of an inflammatory reaction, produced by the pressure of the tumour. In Besnier's, Hess' and Jadassohn's second case, it was absent.

The other constituents of the skin only suffer mechanically. The papillary body and the more or less pigmented ridge net are flattened, the hair follicles now and again diminished, and the sebaceous glands often completely atrophied. When the Myoma is deeper, all parts of the skin, even the coils over it, may be diminished, but are well preserved.

No differences between the smooth muscles and those of the normal skin, in relation to their structure and connection with elastic fibres and nerves, have as yet been noted. The clinical fact, that only the larger tumours are painful, either on pressure or spontaneously, is in favour of the fact, that the pains in these Myomata are dependent, like those of Tubercula dolorosa (false subcutaneous neuromata), on the abnormal tension of a few nerve branches by the enlarging tumour.

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(e). *Chondroma, Osteoma, Cutaneous stones.*

True chondromata and osteomata of the skin are extremely rare, and probably always to be ascribed to aberrant portions of such neighbouring organs as show a tendency to the formation of these tumours (bones, joints, parotid gland, testicles, mamma, etc.). A thorough investigation of the relations of the skin in such cases does not appear to have been made. Probably it is passive, and shows only appearances of compression. So at least does the skin in the single case which I have had the opportunity of examining.

This was a chondroma nodule of the upper lip, of which Dr Formad of Philadelphia kindly sent me a preparation. The skin, with numerous sebaceous glands and a few hairs, is thickened and compressed. In the hypoderm, is a sharply margined, round tumour, encapsuled by dense connective tissue. Its peripheral, younger parts consist of

glandular epithelium, forming tubes and acini, some of which have undergone hyalin or mucous change inside, and, towards the centre of the tumour, pass into irregular epithelial masses. Between the latter is a hyalin inter-cellular substance, still further separating the epithelia, in which cartilage cells appear. The centre of the tumour is entirely occupied by hyalin cartilage, with a few vascular septa. It is thus a subcutaneous hyalin Enchondroma, probably derived from an aberrant portion of a labial mucous gland.

In how far the constituents of the skin itself, especially the glands, form Enchondromata and Osteomata, future investigation must decide. Dolbeau long ago described an Enchondroma of the sebaceous glands.

Much more frequent, especially in old people, is the formation of *cutaneous stones*, that is, nodular deposits of lime in the cutis, still oftener in the hypoderm, which usually show no trace of ossification. But the secondary ossification of such stones has been described (Wilckens, Malherbe).

It is not to be at once assumed that the calcareous stones of the skin all have the same origin, for we know that all sorts of degenerated tissue and inspissated secretion may take up lime salts, and lead to the formation of stone. A special tendency to this, have fat products, for the fatty acids break up the carbonate of lime of the lymph, and form insoluble oleate of lime, and the skin is notoriously rich in fatty products of different sorts. It is therefore the view of Malherbe, that the majority of cutaneous stones develope from proliferated and cystic sebaceous glands, which is very plausible, though there is no actual proof of it.

The first case was described by Wilckens, a pupil of Foerster's, in his dissertation. It was an outwardly stony hard, inwardly brittle tumour of the forehead, beset with masses of granulation, which had existed for thirteen years, in a woman of forty-three.

Wilckens found an alveolar frame-work of osseus tissue, with a fibrillated ground substance, in which clumps of calcareous cells were found. The nuclei of the cells were, some of them, preserved, some of them also calcified, from which Wilckens concludes that the calcification does not necessarily cause the death of the cell, but that, as in the taking up of fat and pigment, the cell may continue to live and grow.

The second case, published by Foerster, showed a simpler structure, roundish clumps of calcified, polyhedric cells embedded in calcified, fibrous tissue.

According to Malherbe, the cutaneous stones, on which he founded the above view, developed usually in women and children; he saw a particularly characteristic one on the ear of a child. They were all

surrounded by a firm membrane, from which septa divided the epithelial contents of the tumour into segments; the contents in all cases consisted of polyhedric cells, most of which were calcified. After decalcification, their protoplasm showed granular and opaque, and did not stain with picro-carmin. The nuclei took the stain, so long as the cells were not completely calcified. Even the cornified cells had taken up lime. Some of the septa, which ran through the epithelial masses, formed, when calcified, true osseus tissue, with fatty or angiomatous medullary canals and Haversian canals, though only after long existence. The younger cutaneous stones were soft, and permeated by hard granules, the older ones as hard as bone; sometimes serous cavities or even abscesses formed around them. Very noteworthy is the statement of Malherbe that he always found giant cells in the septa; he believed that they broke up into a collection of cells and then also calcified. In one case, there was "half embryonic" tissue with giant cells, and myeloplaques round the calcareous mass. Once he saw a calcified epithelioma on the basis of an atheroma; in another case, a calcified epithelioma had developed rapidly after a wasp's sting on the back.

It is evident that Malherbe had no homogeneous material before him, and apparently even several tumours which had formed on an inflammatory basis. In discussing Adenoma of the sebaceous glands, I have already pointed out that, in Malherbe's cases, the origin in the sebaceous glands was only certain in one case. Here I must add that his assumption, that cystic epitheliomata develope from the sebaceous glands and then calcify, also lacks sufficient histological basis. The constant occurrence of giant cells rather points to a development from inflammatory and caseating areas.

A similar tumour to those of Wilckens and Malherbe, was described by von Noorden, which was a stony hard, pear-shaped tumour, the size of a goose's egg, which hung behind the ear by a peduncle two centimetres broad. The skin over the growth was bright red, and showed prominences as large as peas or cherry stones.

The tumour, which was completely encapsuled by a membrane two to four millimetres thick, reached close to the epidermis. From this membrane there passed an alveolar net-work of connective tissue septa, in which the varied lime concretions lay. After decalcification, these were seen to be epithelial collections, in which the nuclei were occasionally wonderfully well preserved. In parts, they looked like concentric horny pearls. There were also a few cells with several nuclei (multinuclear epithelia? Giant cells?). There was no osseus tissue. In spite of its benignancy, v. Noorden thought it necessary to rank the tumour with carcinoma, though his own description shows no reason

for this. Two calcified carcinomata of the scalp, which I examined, showed quite a different structure. The author discusses many other possibilities of development, especially that from proliferating atheroma, without being able to come to any decision. It is at least clear from the cases of Wilckens, v. Noorden and several of Malherbe and his pupils, that there is an anatomically pretty well defined tumour of the skin, which shows slow growth, bony hardness, and a preference for the head (especially the region of the eyebrows), and contains, in a firm membrane, partly or completely calcified epithelial masses, of uncertain origin, separated by calcified or ossified septa of connective tissue. Possibly all these cases were calcified Steatadenomata.

Lewinski suggests quite another method of development of the concretions in his case. It was one of four small tumours of the skin of the scrotum, in a boy of twelve.

The bony hard nodules consisted of firm connective tissue, enclosing rounded or pointed concretions of lime, of various sizes. Where these were separated, one could recognise an endothelium on the cavities, so that the "holes" resembled dilated lymph spaces. Lewinski regards the concretions as calcified lymph thrombi, the tumours as calcified Lymphangiomata. Admitting a certain resemblance with lymphangiectasis, there is no necessary reason for the assumption of calcified lymph thrombi; for many calcareous concretions, of long-standing, form a sort of serous excavation around them, and there was no connection of the spaces with each other or with the other lymphatics of the skin. Clinically, the case has no resemblance to the circumscribed Lymphangioma of the skin, for we would have expected transitions into still existent vesicular protuberances; nor has it histologically, for the cavities were found at the margin between cutis and subcutis. This points rather to a connection with the coil glands and the fatty tissue, than to an origin from the lymphatics, for the dilatations of the latter usually affect the whole skin or only the papillary body. I have therefore not placed this case with the Lymphangiomata.

We see then that the diagnosis of cutaneous stones is easy, but the explanation of their development very difficult. I must admit, that in the single case of cutaneous stone, of the Vola manus, which I had the opportunity of examining, I had to content myself with a diagnosis of probability, as to the genesis.

In this case the epidermis and the cutis, down to the subcutis margin, were quite normal. But here there were various sized, usually long oval calcareous concretions, which, from position, form and size, corresponded either to the complete coil glands, or to individual fat lobules. They were surrounded by capsules of firm

connective tissue, and after decalcification appeared as homogeneous, grey, almost unstainable masses, of irregular form. At the periphery they are often pretty regularly folded, without showing definite remains of epithelia, or any other cells. In some places, coil glands directly margin the concretions, but a definite transition of one into the other was not to be found. On the other hand, some coil glands show distinct and — apparently — regressive changes, which would have been clearer, had not the decalcifying fluid (picric acid and nitric acid) rendered a good protoplasm stain impossible. The epithelia of the coils were enlarged at these places, still more difficult to stain than the others, and the form of the loops was irregularly stretched. In other places, several adjacent loops have run together into a broad, irregular epithelial mass, or they may be greatly compressed and atrophied. With the methyl-blue-tannin stain, a few nuclei may be recognised at the periphery and even in the middle of these calcareous islands. These may belong to coil epithelia, just as the large, badly stained epithelia of the coil may have been calcified. But these facts are no proof of a primary calcification of the coils. The nuclei of the collagenous sheaths, lying next the calcareous islands, are very distinct, and, when they enclose vessels, very abundant; they may very well explain the nuclear remains in the calcareous islands.

So much only is certain, that the calcification is ever affecting, in islands, larger stretches of the subcutaneous tissue and the lower layer of the cutis, by which territories, about the size of the coils or the small fat lobulas, are all at once calcified, and adherent like peninsulæ to the large concretions. Then it is clear, since there are here no other constituents of the skin, that the calcification affects only fat lobules, and coil glands so far as they are enclosed in fat lobules; the still unaffected fat lobules at the side of the concretions all contain some loops of coil glands. But whether the coils outside the fat calcify, or only degenerate from the pressure of the concretions, is as uncertain as the point of development of the whole affection. Giant cells and inflammatory products are not, in general, present; otherwise one would think of a calcified residue of some previous suppuration in the subcutaneous tissue. But possibly there is also a specific degeneration of the coils.

I have given these observations thus fully, though they are neither clear nor unanimous, in order to draw the attention of future investigators to this difficult and interesting subject. It is of especial importance to use such methods of decalcification as do not destroy the finer histological structure.

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(β). Stagnatory Tumours.

1. *Stagnatory tumours of the epidermis.*

(a). *Keratoma.*

The position of the keratomata in the section of stagnatory tumours, although, on account of the absent power of production of true horny cells, strictly correct, requires justification, in view of the ready objection, that the Acanthomata also (*e.g.*, Verruca, Epithelioma contagiosum) are frequently accompanied by thickening of the horny layer, and that, in the course of development, a tumour of the prickle layer may become a horny tumour. It might then be better to have no special class of Keratomata, but to divide the Acanthomata into two divisions of more or less cornified epidermic tumours. Such an arrangement of the Keratomata under the Acanthomata would not be in accordance with fact, for there is a series of well-characterised Keratomata, the callosities and corns, in which the horny layer is primarily thickened, and the prickle layer not at all, or only very little secondarily hypertrophied. These at least must be separated, and form a distinct class of Keratoma. Then we must reflect, that an Acanthoma *may* certainly be partially converted into a Keratoma (Verruca) but by no means *must* (Condyloma). Acanthosis and hyperkeratosis are, as I have so often remarked, completely independent processes, which, even where they are combined, are not dependent on one another. If then we are compelled to form, and justified in forming, a separate division of the Keratomata, it appears advisable to include in it all these epidermic tumours in which the excessive horny formation far exceeds the acanthosis (Cutaneous horns and Onychogryphoses). Finally, this division, of course, includes those affections in which nothing but hyperkeratosis is definitely established (Keratodermiæ).

In describing the Acanthomata, I have indicated it as a distinct advance, that we have abandoned the half-way house between cutaneous

and epidermic tumours, the hybrid division of the so-called "papillomata," in favour of the group of Acanthomata. It may therefore appear inconsistent, that I should describe among the Keratomata certain mixed tumours, in which hypertrophies of the cutis are combined with epidermic hypertrophy. But on close consideration it is clear, that the definition of mixed tumour has here quite a different meaning from what it has in the so-called "papilloma," where a presumptive papillary growth was recognised as sufficient ground for a secondary epidermic thickening. I am only referring to the occurrence of Keratomata on a limited area of skin, which has previously suffered a tumour-like change. It is then a mixture of tumours of different nature on the same area of skin. Thus a cutaneous horn may develope from a small pendulous fibroma (Fibro-keratoma) or from a capillary varix of the papillary body (Angio-keratoma); in both cases, there may be no Keratoma. There thus exists, between the two tumours, no necessary connection. Since they are on the same seat, they are influenced to a certain degree by, but do not necessarily induce each other. They may therefore be treated of with the rest of the keratomata, without founding a special half-way house between epidermic and cutaneous tumours.

Callus, Callosity.

Callosities are circumscribed regular thickenings and condensations of the horny layer, which pass gradually at the border into the healthy tissue, and in which the epidermic marking and the sensation of touch are less distinct than normal. Their commencement is always traumatic, and they are usually induced by pressure, not that scaling is simply prevented, but the pressure welds together the horny substance, so that its cellular structure is largely lost. Heat, alkalis, and strong acids produce a similar welding, and lead to callosities. By prolonged rubbing during the welding, exfoliation vesicles develope instead of callosities. The callosities from tight boots are seated over the heads of the phalanges and metatarsals, on the big toe, behind and beneath the heel; the trade callosities have been carefully described by F. Hebra. Bursæ frequently correspond to callosities, simply because they are formed at the same place; there is no direct relation between them.

The spontaneous callous thickenings of the horny layer, I regard, not as callosities, but as Keratodermiæ. In them the welding is independent of external pressure.

When they last longer, and the pressure is intermittent (particularly, then, in the callosities of the feet), there is formed at the base an inflammatory, or apparently inflammatory condition (see traumatic inflammation).

Histologically we find, at the commencement, changes only in the horny layer. The terminal (superficial layer) is thickened and condensed. Normally, it consists of dead, a-nuclear, exfoliating horny cells, which, with picro-carmin, take a yellowish-red, spotted stain.

The broad, terminal layer of the callosity shows a pure yellow colour, is more deeply stained, and has no red dots. It has consequently become more homogeneous and denser. With an orcein or fuchsin stain and decolourisation with creosote, we see the nuclear fragments, which were invisible in the middle layer, once more distinct. The sweat pores, in the welded terminal layer, become indistinct or disappear altogether. Naturally the condensation of the outer horny layer is accompanied by a diminution of scaling, and therefore the middle layer of the horny layer is, more or less, often distinctly widened. In this loose layer, the sweat pores are dilated and run through the callosity, in broad loops, up to the terminal layer; they are sometimes laterally bent along with the whole horny layer. Their dilatation must be regarded as a stagnatory phenomenon, on the one hand, of the secretion retained below the terminal layer, on the other, of the displaced lining of the walls of the sweat pore. The granular layer also is usually thickened, but the prickle layer is almost always flattened, in comparison with the healthy neighbourhood, the ridge net often completely flattened out, and the papillary body wavy. In no case is the papillary body, at the commencement of the callosity, hypertrophic. But it is different in the chronic inflammatory, "inflamed" callosities. Here we find a hypertrophy of the prickle layer, especially the inter-papillary, on account of the persistent pressure of the welded horny layer. Thus long papillæ are furrowed out; these are often laterally bent, as is the ridge net of the epidermis, or inclined to one side. We also find a dilatation of the superficial capillaries, and a multiplication of the spindle cells of the papillæ, especially around the vessels. Only this last indicates, histologically, a very very slight inflammation. The acanthosis and the consequent papillary enlargement are not to be distinctly regarded as such, for they may also be the results of normal epithelial proliferation, with stagnating horny layer, or finally, a sign of a non-inflammatory acanthosis. But if these secondary appearances are of doubtful nature, the first stage is merely a non-inflammatory thickening of the horny layer.

Clavus, Corn.

A more developed callosity, whose centre enters the cutis in the form of a conical tap, and is painful whenever touched. The welding, which is only superficial in the callosity, here goes deep, and leads to the separation of the central part of the callosity from the peripheral. In the central core, the horny layer unites into a hard transparent mass. If a core has formed, the growth of the epidermis provides for its continual increase, by adding to it, from beneath, newly welded plates of horny substance. The basis and surroundings of the corn are always hyperæmic. The cutis beneath the corn is atrophic, but never completely gives way, except when suppuration is added.

Clavus shows at its periphery the conditions of the skin, described of the secondary stage of the callosity, from which it proceeds. Here the prickle layer is thickened, as is the granular layer, and towards the centre of the corn, the central horny layer, while the terminal layer shows evidence of welding. The sweat pores run through the epithelium, dilated, and showing many windings. The papillæ are enlarged, and their blood vessels dilated.

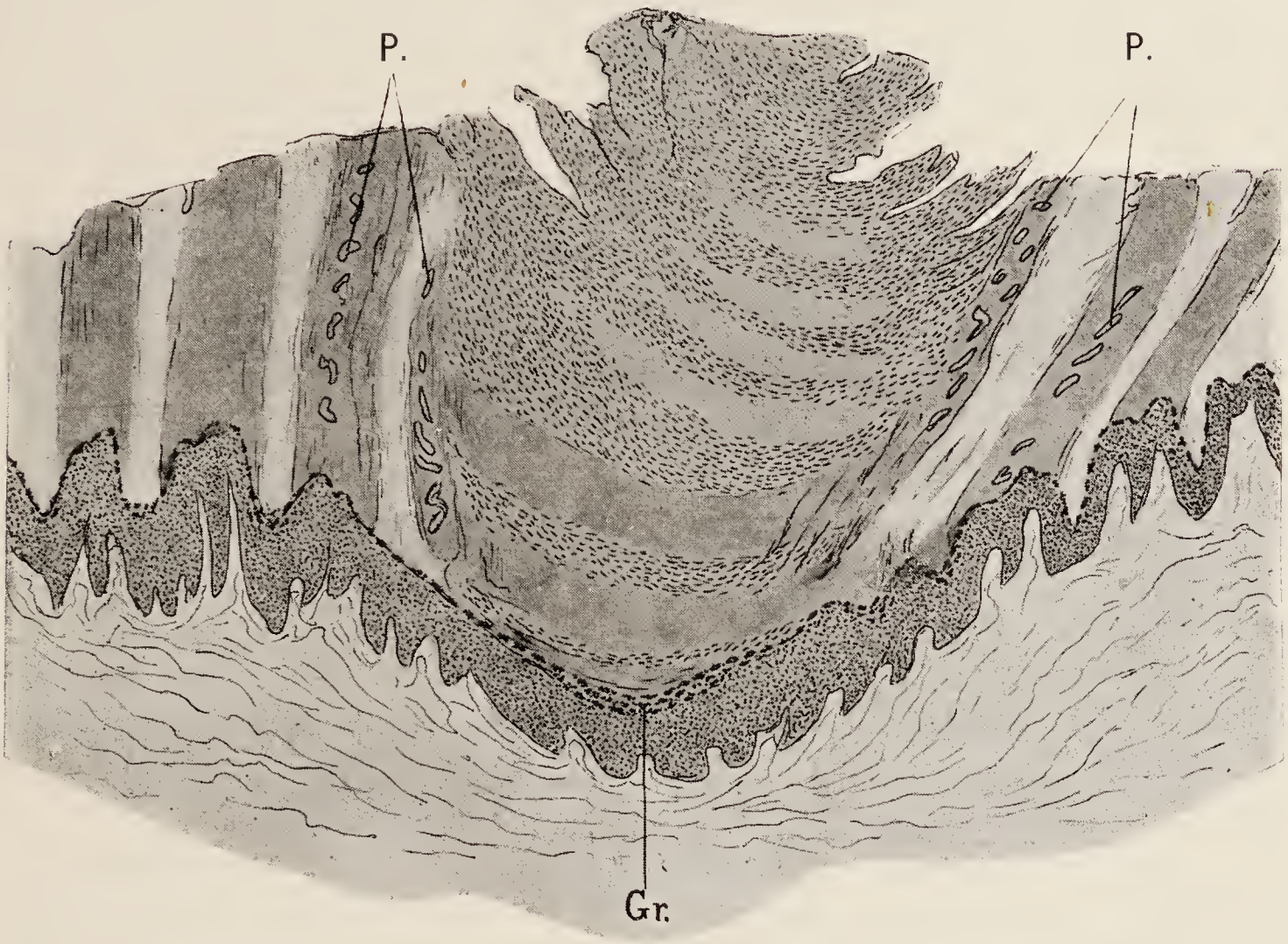

FIG. 30.—Clavus.

Tap-like process of thickened and condensed horny layer, showing zones of simple and maximal compression, the papillæ largely obliterated, the granular layer *Gr.* at the stage of thickening, the pores *P.* winding dilated through the horny material.

The core is quite different. Here the ridge net and the papillary body are once more flattened. Sometimes a few large papillæ are found in the centre of the core, with corresponding ring-formed ridges, which have resisted the pressure of the central horny mass surrounding them. The latter may enclose a well-preserved sweat pore, which may be followed to the core. This consists of compressed horny layer, in which the leafy structure is in many places completely lost; there are formed blocks and plates of transparent horny substance, which in the sections are easily loosed from their connections, and whose composition from individual cells is hardly recognisable. As a whole, the core has a conical form, pointed beneath. It is

surrounded by the middle horny layer, and presses, with this, the papillary body and the ridge net downwards, deeply excavating them. At the same time—as usual under pressure—the granular layer beneath them disappears, and the general flattening of all the epithelia may so increase, that the margin between the horny cells and the flattened prickle cells is no longer recognisable.

On the cutis, pressure of the clavus has the result, that the papillary body is replaced in the centre by a depression, while at the side of the core the enlarged papillary body is obliquely laid and displaced. The ducts of the coil glands are also affected and usually dilated, often like beads. The coils are well preserved, only their lumen is usually dilated. Even those glands whose pores disappear in the core do not atrophy—a noteworthy fact regarding the function of the gland. Nor does the fatty tissue atrophy, where it is normally present. The collagenous tissue under the corn is pressed together and condensed, the elastic tissue gradually completely disappears. The sweat pores deserve special notice. At the side of the core they are all, as noted above, well preserved, frequently dilated and bent, as they describe an arch or an obtuse angle around the core. In the core their behaviour varies. Some of them penetrate even to the densest central part, but most of them are distorted, blurred and indistinct, or they stop suddenly at the border of the horny clumps, which then appear as if they had developed from the epithelia of the sweat pore. One therefore finds in the core of the corn fewer sweat pores than would be expected.

Where, underneath the core, a few papillæ happen to persist, there are sometimes found, over their apices, groups of red blood corpuscles or leucocytes enclosed in the core, which are due to a lesion of these exposed papillæ.

By using different stains (hæmatoxylin and acid orcein, fuchsin with creosote decolourisation, iron hæmatoxylin) Dr Müller found, in my laboratory, a peculiar behaviour of the epithelial nuclei in the centre of the core of the corn, in which two different degrees of compression of the horny cells could be distinguished: (1) simple compression, whereby the cell margins become indistinct but the nuclei remain evident; and (2) maximal compression, with simultaneous distortion and displacement of the layers, and appearance of isolated blocks and fissures. In this the nuclei again disappear, and the horny substance shows, with many stains, a different tinge. These zones of greatest compression alternate with those of simple compression, or run through them in irregular wavy lines, and thus, with an appropriate stain, the core of the clavus has a marbled appearance.

A secondary change in the corn, which is not necessary to it, and

usually developes from external maceration, is the giving way of the terminal layer, by which the welded central parts are arranged in terraces, over the level of the skin, like an oyster-shell.

Cornu, Cutaneous horn.

The horny excrescences known as cutaneous horns have only an outward resemblance to the horns of animals (apart from the horn of the rhinocerus), and have not their hardness ; their consistence is about that of the normal or gryphotic nail. Longitudinal lines on the surface, and medullary, softer lines on longitudinal section indicate, even macroscopically, a papillary formation. The colour is, like that of all horny substance, yellow, brown to black, more or less transparent to completely opaque. The length depends on the nature of the matrix and the hardness of the horn. The smallest thorn-like ones are the fibro-keratomata, the largest are the size of the horns of small animals. The thickness varies from that of a slate-pencil, or a finger, up to a diameter of an inch. On section they are angular, oval or round. The more band-shaped they are, the more spiral is their growth. They may be completely isolated, or surrounded by smaller and minute ones, with which they sometimes unite. They usually develope late in life, increase rapidly up to a certain size, when growth is arrested or advances more slowly. As in many keratoses, there are often ebbs and flows, with periodical arrests in growth ; these intervals are indicated externally in cross furrows and tile-like projections. At such places, near the root, the horn often breaks off and then grows again in the old way. But they are not thrown off regularly, as in moulting. In 109 cases, Lebert found the cause in 39 pretty clear ; in 27 the origin was a warty spot. I have observed small, isolated, fibromatous nodules as the origin of certain very small, multiple cutaneous horns, on the necks of old people, usually women. The preference of cutaneous horns for the seborrhœic regions of the skin, the hairy scalp, forehead, the nose, the eyelids, the glans, the testicles, is somewhat remarkable ; as is the seborrhœic history of many of them. The two forms of warty outgrowths, the acuminate condyloma and the seborrhœic wart, which also share this preference, frequently form the starting point of cutaneous horns. Then many horns clearly develope from dermoids and atheromata. This, of course, is no proof of a follicular origin (Lebert) of the cutaneous horn ; for dermoids and atheromata are not cysts of the sebaceous glands, and the sebaceous glands cannot produce cutaneous horns, for, as soon as their fat production is arrested, they once more act like surface or follicle epithelium. Sebaceous fat in the cutaneous horns, if present, would only show that the hairs and sebaceous glands had not perished in the production of horn. Even in the atheromata, a warty excrescence of the follicle wall forms the basis of the horn. As the cutaneous horns gradually pass into the healthy tissue, it appears as if they were seated superficially on the skin, while at the sudden, steep transition, we observe a circular depression, and note that the new structure is deeply rooted in the skin, with thick epithelial ridges. This "moat" developes by the falling out of a peripheral horny mass, in the form of a rim round the horn. It has, like the presence of cutaneous horns in atheroma, led to the unfounded view that some of the cutaneous horns are of follicular origin. The true cutaneous horns always show on section, softer medullary spaces (Simon, Virchow) and—in connection with this—a papillary trunk and a steep wavy lamellation. It would be advisable, on anatomical

grounds, and clinically possible, to separate these horny excrescences which have the structure of a-medullary callosities consisting of even lamella, and only outwardly resembling, by their elevation, the cutaneous horns, from these (as false horns, keratoid, or other specially-named keratomata). Although the true cutaneous horns always show a papillary form, the presence of normal papillæ is not necessary for their development, for horns may develope on scars. A development from the sweat glands (Lebert) is absurd, as Rindfleisch has already shown.

All my cases of cutaneous horn (six Fibro-keratomata, one horn from the eyelid, two from the face and, one from the penis) showed the same structure; they were *papillary and medullated Keratomata, growing on a circumscribed, warty base.* In the Fibro-keratomata, an ensnared fibromatous nodule formed the base; the larger horns of the eyelid, penis, and face were preceded by small, hard, acuminate warts, like condylomata. Since the genesis of the horn is clearest in the fibro-keratomata, where all stages of development may easily be observed simultaneously in different growths, I will discuss the development of the horn from this text.

There are two stages of horny formation, of which the first is characterised by a *simultaneously developed acanthosis and hyperkeratosis,* while the second stage, that of the complete horn, shows *advancing keratosis, with diminished acanthosis.*

The epithelial growth of the first stage leads to the formation of a hypertrophic ridge net, and seeks, since the simultaneous increase in horny cells, the basis of hyperkeratosis, opposes its extension outwards, an escape, in dense epithelial ridges and taps, downwards into the cutis. The formation of this ridge net, and the taps springing from it, is decided, like the formation and number of the persistent papillæ, by the behaviour of the papillary body at the commencement of the advancing epithelial growth. In some cases the acanthosis leads at once to an increase of the inter-papillary prickle layer; the papillæ which are present, whose resistance must be assumed to be considerable, are respected, and their number in the later horns is the same as that of the areas of skin which form their base. Only their form is altered; they are unusually elongated and thinned, thread-like. Sometimes they are secondarily furrowed by lateral epithelial ridges and taps; thus are formed the so-called daughter papillæ.

In other cases, where the resistance of the papillæ is, all along, less, they are mainly flattened out by the pressure of the epithelium, as at the commencement of an ordinary wart. Only a few remain, and are deformed as described. Thus the cutis is furrowed out under the pressure of the firm horny shell which covers the whole growth, in a new and irregular fashion, by individual epithelial taps, more rarely by

ridges, and thus the number of papillæ in the cutaneous horn is again increased, though not to what it was before.

As we see, there is no definite relation between the pre-existing papillæ and those of the cutaneous horn. The latter, as G. Simon noted, contains in most cases many fewer papillæ than the corresponding area of skin. The deformities and branching of the papillæ are only secondary results of the epithelial growths, and develope passively.

While thus, on the one hand, the abnormal cohesion of the horny cells drives the processes of the prickle layer downwards, it causes, on the other hand, a pressing of the parallel horny mass outwards, and thus the small growth becomes a horny, transparent, but still rounded ridge. The granular layer is usually widened. There are no signs of inflammation in the cutis.

When the epithelial taps have grown through the cutis, have reached the base of the tumour, and have almost united, so that the connective tissue trunk is reduced to a thread-like papilla, the second stage, the formation of horn proper, begins. The epithelial growth is now much slower, while the cornification goes on increasing. Since the cornified layers, in virtue of their abnormally firm connection, cannot be thrown off, there developes an ever higher cylindrical, horny mass, about the diameter of the fibroma beneath. The characteristic structure of the cutaneous horn is due to the fact, that cornification does not extend equally, but is in different degree in the inter-papillary and supra-papillary areas. Cornification is simplest in the parts between the papillæ, where the horny layer sinks down deepest, and thus takes the form of a serial set of filters or wedges. Underneath these horny wedges, the broad granular layer gradually diminishes, entirely, or to a single layer, and the prickle layer also atrophies, at this deepest point of the cutaneous horn, to a thin flat shell. The horny cells of these parts of the cutaneous horn have, in their consistence and tinctorial quality, the character of basal horny cells or of nail cells; they represent the firmest portion of the horn. In some places, especially in the upper parts of the horn, there is a firmer welding of the horny cells, so that they appear quite homogeneous. Here and there, in making sections, there break from these homogeneous places, pre-formed, round, dove-tailed fragments, some of which are hyalin. In other places there are regular horny pearls, sometimes in areas of microscopic and macroscopic size.

The form of the cells in the supra-papillary areas of the horn varies much more. Here also the granular layer disappears, even beneath the papillary apex, at the neck. So far, on the sides of the papillæ, it may usually be followed. The head of the papilla is usually

surrounded by indifferent, usually cubical, small prickle cells, in which the prickles are very indistinctly formed. Then, instead of granular cells, come very much swollen, fibrinoid-looking, granular, or finely-fibrillated, a-nuclear cells, which stain deeply in hæmatoxylin. Then in place of the basal horny cells, we find quite homogeneous, somewhat shiny flakes, staining less with hæmatoxylin, representing whole cells,

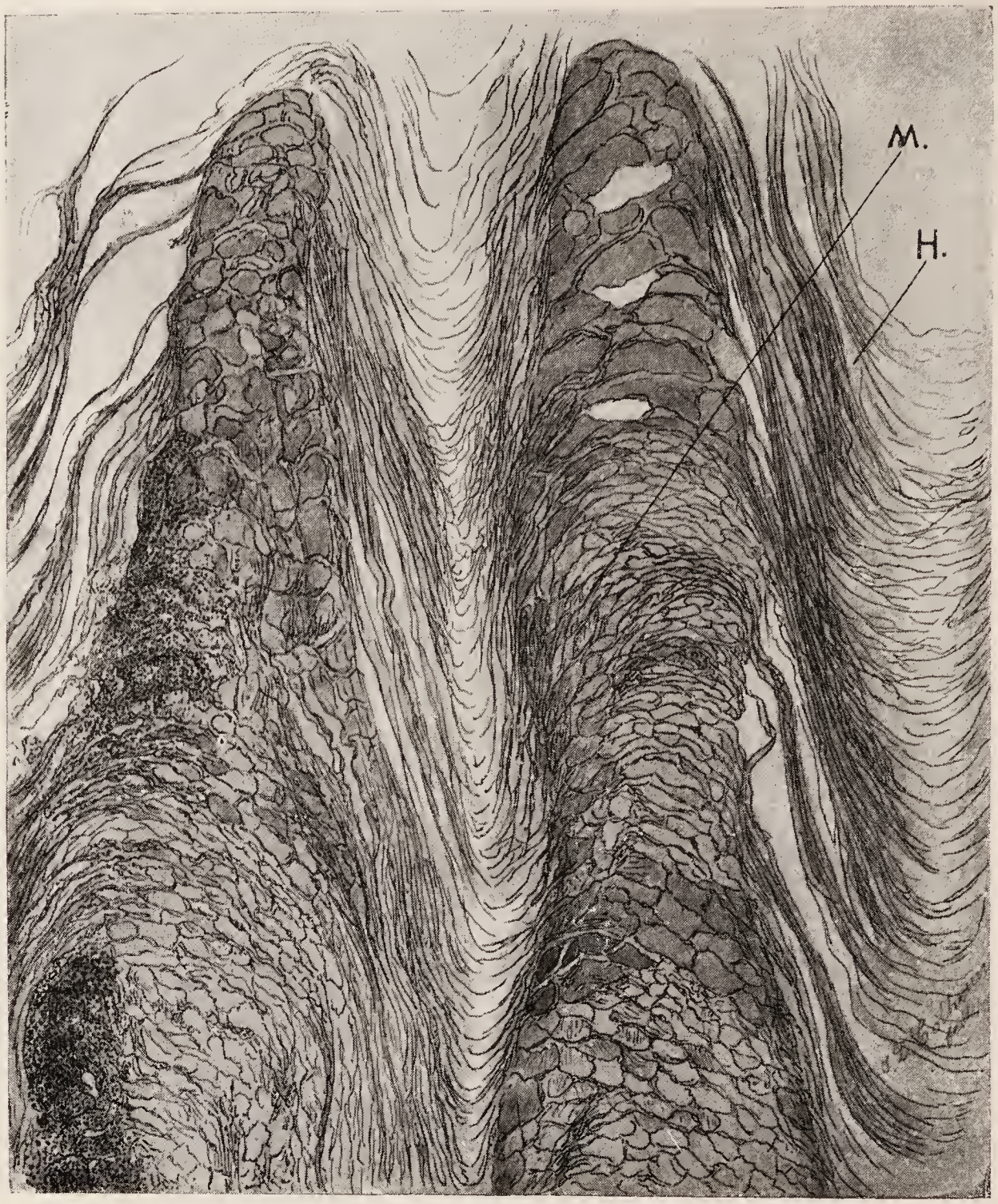

FIG. 31.—Cutaneous horn, showing degeneration over two papillæ.

H. Horny layers.

M. Medullary centres, which contain darkly-stained, homogeneous material, and that to the left in some places very darkly-stained fragments of nuclei, possibly those of wandering cells, or nuclear degeneration of cell contents.

though in section only round or oval portions are visible. Above these, perpendicularly outwards, are, sometimes the same clumpy, homogeneous fragments, sometimes hollow cells, whose homogeneous contents are absorbed, and permit the entrance of air, while the

horny cell mantle remains. Thus over most of the papillæ, there is a "medullary" column of cells, penetrated by spaces. Some of the papillæ have a column, formed only of hollow cells, which are usually separated by buttresses of homogeneous clumpy masses. But usually, in the exactly supra-papillary regions, flakes and hollow cells vary irregularly. In addition to these two degenerated products of horny cells there is another degeneration, which I first described in 1879 in connection with cutaneous horns, under the name "nuclear degeneration." In it, the swollen cell is often densely filled with coarse granules and fragments, which stain deeply with hæmatoxylin, like nuclear fragments. The nucleus disappears, and the nucleoid fragments are far too numerous to be regarded as its products. It must be some nucleoid degeneration product, developed from the cell protoplasm, with perhaps the assistance of the liberated nucleic acid of the nucleus. Of course, in cutaneous tumours which are exposed to frequent injuries, leucocytes may wander from the papillæ into the hollow cells of the horn, and fill these with nuclear fragments; red blood corpuscles and masses of blood pigment are often enough found in the horny masses. But the nuclearly degenerated horny cells are found quite independent of these accidental, traumatic influences.

The alternating supra- and inter-papillary longitudinal streaks of cutaneous horns were previously described as columns or palisades. G. Simon distinguished a medulla and a rind, as in the hair, but it must be noted, that the medullary substance of the horn is by no means limited to the central parts, but is irregularly distributed, corresponding to the irregular arrangement of the papillæ in the horn. *Only so far is there a regularity*, that, in longitudinal sections, inter- and supra-papillary streaks of very different widths alternate, and the word *medulla* is only due to the fact, that this partly hollow and softer horny substance is always formed *only above a papilla*.

To get a clear idea of the development and arrangement of the cutaneous horns, it is well to divide the horny mass into horny wedges and horny cupolæ. The sets of horny wedges sink down into the epithelial taps and ridges, fill the spaces between the persistent papillæ, and are united above into a connected horny mass by the cupola or thimble-shaped horny sheaths over the papillæ. Only inside these horny sheaths is the so-called medullary substance formed.

As we see, there is no resemblance between the formation of the cutaneous horn and the callosity. The distinction between them is due to two main differences. First, the formation of the callosity is caused by an artificial, outward welding and hardening of the horny layer, while the cutaneous horn owes its development to the abnormal adhesion of the cornified cells. Then in the callosity, the epithelial

growth is only secondary, while in the formation of horn it is simultaneous with the hyperkeratosis. Thus the cutaneous horn always has a papillary formation, which is never flattened out by the gradually increasing hyperkeratosis, but can only become more persistent.

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Angiokeratoma.

A mixed tumour, appearing on the hands and feet of young persons, on a basis of perniosis or local asphyxia, and consisting of capillary ectases, with a keratoma over them. At first there develope red spots, which disappear under pressure of the diascope, and therefore represent ordinary capillary dilatation. Among them gradually appear larger capillary varices, which no longer disappear under the diascope. Above them the epidermis, and especially the horny layer, thickens, so that a transparent keratoma developes, with bloody areas shining through, which looks like an ordinary wart. These Angiokeratomata are sometimes isolated, sometimes in groups, especially on the backs of the fingers, where they run together to larger, grey, dry, warty patches, in whose bases a few bluish-black points are evident.

Mibelli has given us a thorough description, both clinical and histological, of the affection. According to him, the process commences at the small red points, with dilatation of the capillaries of the papillary body. These expand so much, that the neighbouring epithelial ridges are compressed and diminished. At the same time the spaces of the middle and deeper layers of the cutis are dilated, and some contain red blood corpuscles. The blood capillaries over the same area are also somewhat dilated. A few emigrated leucocytes indicate the commencement of an inflammatory change of the cutis. Mibelli found the prickle layer unaltered, but the granular layer very much widened, and the basal horny layer rich in elëidin. The horny layer, except for its widening, was normal, and showed normal sweat pores.

At the height of the affection, in the centre of the larger warts, the papillæ were mostly transformed into cavernous blood spaces, which sometimes simply filled the papillæ, sometimes were divided by septa. The same blood spaces were found as far up as the prickle layer, and even in the horny layer, while, on the other hand, the prickle layer between the blood spaces, sent long, thin, sometimes

branched epithelial processes into the cutis. Above some of the blood spaces, there were found, inside the horny layer, signs of serous exudation and medullary formation.

In addition to these appearances, Pringle found noteworthy deviations. The inflammatory infiltration with leucocytes, and the thickening of the collagenous tissue in the papillary body, were more marked. But Pringle was unable to find, in his preparations, dilated lymph spaces filled with blood, nor did he find serous exudation in the horny layer, or medullary formation. The sweat pores were distinctly narrowed, and there were no sebaceous glands in the tumour. Pringle lays more weight on the deep growth of the prickle layer than Mibelli.

Like Pringle, Joseph found the sweat pores narrowed, only where there was compression, otherwise normal. Like Pringle, he observed neither lymphangiectasis nor medullary formation. Otherwise he describes the changes like his predecessors; only he speaks, strangely, in his clinical notes, of "extravasation" in the cutis, instead of angiectasis; for the assumption of extravasation, even his own description supplies no histological ground.

From preparations kindly sent to me by Professor Mibelli and Dr Buzzi, I can confirm almost all the changes described. It is beyond doubt a punctate venous ectasis, developing on the basis of a general stagnation, in whose centre larger capillary varices appear in the papillary body. They form primary points of blood, over which the epidermis is visibly and perceptibly thickened. The secondary, not very marked acanthosis, induces, in common with the swelling of the varicose papillæ, the elevation of these blood points over the level of the skin, to which succeeds, as a third stage, the horny formation due to the addition of hyperkeratosis. While Mibelli's preparations enabled me to confirm the formation of areas of softening and medullary cavities over some papillæ, which were in no way different from those in cutaneous horns and in onychogryphosis, in the preparations of Buzzi, the advance of the blood spaces from the papillæ into the prickle and horny layer, the process of epithelial bleeding, could be recognised. At first, the still persisting, sub-epithelial marginal layer runs together, and the cavernous blood spaces are directly surrounded by prickle layer, which, in contact with the blood, is converted into hyalin flakes. Sometimes these run together into hyalin stripes, which then bound the varix; sometimes the blood, pressing the prickle cells asunder, makes its way to the horny layer. Before that, the otherwise very broad granular layer disappears over these advancing angiectases, and we have, in the horny cupolæ over such papillæ, moderate softening and cavity formation, while other horny cells of the basal layer

form very refractile hyalin clumps. In these cavities, in the same way, only in greater extent than in cutaneous horns, bleeding takes place over many of the papillæ, its route being indicated by the spongy, bloody remains of the prickle layer over the varix. The blood spaces in the horny layer have almost always a definite seat—over the varicose papillary vessels—and a definite form, almost concavo-convex, corresponding to their fitting into the horny cupola and their excavation over the papillæ. During this extension of blood in the epithelium, the latter shows—I agree with Mibelli—only passive appearances of compression and degeneration, but none, or at least very slight epithelial growth. The angiectasis would evidently reach the surface and give rise to hæmorrhage, were it not that a new factor stepped in, an abnormally great cornification of the epithelium. This leads to the formation of a keratoma, a miniature cutaneous horn, which only shows an outward resemblance to the ordinary wart, its structure and development being very different from it. In particular, in this keratoma, there is no great and persistent acanthosis.

A very useful comparison would be that of Angio-keratoma with that change of the cutis, which I shall have to describe among the results of varix of the leg. While there the elastic tissue prevents the penetration of the varix into the defenceless collagenous tissue of the cutis, here the horny layer opposes its entrance into the epidermis. The whole form of Angio-keratoma does not give the impression of a primary epithelial growth, but of a stagnatory dermatosis on an angio-neurotic basis, and so we see histologically, that the slight acanthoma formation at the commencement is without special significance, and the secondary keratoma formation is only marked when the stagnation reaches the epithelial margin. The stagnation of the horny mass is the answer and reaction of the epidermis to the stagnation of blood in the papillary body; in this sense, the name, Angio-keratoma, is completely justified.

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Other Keratomata.

Under the name *symmetrical keratodermiæ of the extremities*, Besnier has described a symmetrical thickening of the horny layer of the palms and soles, which developes in youth, is independent of employment, and, better or worse, lasts throughout life. The hyperkeratosis appeared in islands on the palmar

surfaces of all the fingers and toes, and on the projections of the palm and sole, and the hyperkeratotic areas are separated from the healthy surroundings by an erythematous zone, ½ centimetre broad.* In slight cases, the normal relief of the horny layer is preserved and thickened ; where more developed, it is lost, and the nail-like, homogeneous horny rind is covered with irregular dimples, furrows and painful rhagades ; otherwise the affection is painless. There is no eczema, and no disturbance of sensation. There is often hyperidrosis. Besnier suspects a central nervous origin ; he distinguishes from the ordinary form of this dermatosis, one appearing in multiple small areas.

Balzer had the opportunity of examining the horny layer in one case, and found, in the yellow-stained (picro-carmin) horny mass, a great number of carmin-stained collections. The sweat pores in the horny layer were dilated, and some linear fissures reached to the prickle layer. The horny mass was very refractile and homogeneous, and the cell margins were as difficult to demonstrate as the nuclear remains. Among them there were some spaces, which had the appearance of felt-work (medullary substance ?). In the neighbourhood of the sweat pores, the horny cells were compressed into flat bundles. According to Besnier's description, which lays stress on the surrounding erythematous zone, it would appear as if we had to do with an anomaly of cornification, and as if the infection rather belonged to the dry cutaneous catarrhs. Nevertheless Besnier ranks it with the Keratomata, and from my observations I must regard this non-constant, peri-basal erythema as a secondary phenomenon, such as in many cases accompanies callosities. Histological investigation has to clear up two points: first, which change in the initial stage is primary, and second, how the horny layer behaves, where it is not welded by external means. In other words, investigation must establish the differential diagnosis, from the dry cutaneous catarrhs on the one hand, and callosities on the other.

Brooke has recently described an external, somewhat similar affection, which he calls *erythema keratodes symmetricum*, and which represents a sub-acute, easily healed affection. It is definitely preceded by a sharply circumscribed erythema of the palms and soles; then there developes a superficial hyperkeratosis of these regions, accompanied by marked œdema and greater tenderness. At the same time, there appear, on the extensor sides of the finger-joints, a few erythematous horny nodules. This form of hyperkeratosis, in distinction to Besnier's affection, is probably primarily inflammatory. There are yet other forms of hyperkeratosis, which are limited to the palms and soles, such as those after the use of arsenic, and after prolonged hyperidrosis. But as yet they have

* I have seen this erythematous area in several cases.

not been histologically examined. Finally, we must mention the allied congenital conditions of Keratoma palmare et plantare and Acrokeratoma hystriciforme hereditarium (the former, see under malformations).

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Onychogryphosis.

The claw or horn-like deformities of the nails, accompanied by excessive accumulation of horny substance, are, strictly speaking, not simple hypertrophies of the nails, as is usually taught, but keratomata of the nail bed, combined with keratoid hypertrophy of the nail plate. One has only to reflect what sort of appearance true, simple hypertrophy of the nail would present, to see at once that it is by no means easy, and were it really to occur, would hardly be described as hypertrophy of the nail.

It has always been understood that, in speaking of the hair, one meant the shaft alone, without the root sheath. In the case of the nail we have been still more lax, and by the nail have understood, sometimes the nail plate alone, *i.e.*, the nail proper, corresponding to the hair shaft, sometimes the nail with its surroundings, *i.e.*, with the horny layer of the fold and of the nail bed. A result of this loose way of speaking is, that all collections of horn in the region of the nail are shortly described as hypertrophies of the nail, and a thorough analysis of the appearances becomes impossible. Hypertrophy of any epithelial area only appears, as noted in the introduction, where epithelial proliferation exceeds the exfoliation of horny substance, This general law, applied to the nail, shows that we can only speak of simple hypertrophy of the nail, where the nail cells proliferate more actively, or their coherence increases. The proliferation of the nail cells is, in comparison with the surrounding prickle cells, normally very active, as is seen from the necessary frequent cutting of the nail, in comparison with the desquamation of the surface epithelium of the ungual phalanx. In view of the small area of skin which the nail matrix occupies (posterior nail fold up to the border of the lunula), its constant production of horn must be regarded as wonderfully great. An increase of this factor is consequently not to be readily expected, and it could only grow, noticeably, by an increase in the size of the nail matrix, this growing further into the posterior or lateral folds. A broader and thicker nail plate would

then develope. This, as an independent affection of the nail, has apparently not yet been observed; but such an enlargement of the nail matrix, with consecutive thickening of the nails, appears along with Giantism and Acromegaly. Only these cases can be regarded as simple, true hypertrophies of the nail.

The cases of accelerated nail growth, measured by the necessity of frequent cutting of the anterior border, or the more rapid advance of marked points on the surface of the nail, are therefore only to be accepted with caution, as proof of an increased nail production, and would, even where nail hypertrophy existed, hardly be regarded as a proof of it, for we are not in the habit of leaving the nails uncut, and thus indicating nails of greater length as hypertrophic. Indeed, even in the Chinese custom of leaving the nails uncut, a more rapid growth at the matrix would not necessarily lead to longer nails, for with the more rapid advance, correspondingly rapid separation and pointing might take place at the anterior end, and thus no elongation of the nail. Most cases of accelerated advance of the nail plate are not to be attributed to an excessive existence of nail cells, but are only produced by a narrowing of the posterior nail fold. This always causes thinning of the nail plate, and therefore, production being the same, induces a more rapid advance along the fingers. It often accompanies, for example, the clubbed fingers of consumptives or those suffering from heart-disease, when the general nutrition of the epithelium is not affected. And in the inflammatory skin diseases (Eczema, Psoriasis, Pityriasis rubra pilaris) of the ungual phalanx, the increased necessity of cutting the nails is not always the result of increased growth, but more frequently of the narrowing of the posterior fold, caused by swelling of the cutis.

In contrast to the simple elongation of the nail, which is hardly ever observed, its shortening, paradoxical as it may sound, more often leads to the diagnosis of hypertrophy, in the cases where it is accompanied and caused by a thickening of the nail plate. For, as the thinning of the posterior fold, or the narrowing of the fissure from which the nail comes, results in thinning and more rapid advance of the nail plate, a dilatation of the posterior fold, or the fissure, results in its thickening and slower advance. In such cases, the convex roundness is partly or completely lost, the nails become thicker, firmer and flatter, their longitudinal lines are more distinct, and they advance as slowly as the big toe nail. Up to a certain degree of development, these thick, even nail plates are normal, and are, just like finer, better rounded ones, hereditary, or they may develope in later life with a corresponding change in the ungual phalanx. But, more marked, this thickening, with slower advance, accompanies certain cases of those

inflammatory skin diseases of the ungual phalanx (Eczema, Psoriasis), which, under other circumstances, induce diminution of the posterior fold, and thinning of the nail plate.* Then it is frequently the result of mechanical labour, in which pressure on the finger pulp, from beneath and before, gradually widens the posterior fold. In all these cases the nail plate is thickened, less shiny, uneven, but not altered in colour and consistence.

In this form of thickening of the nail, with slower growth, there is, no more than in thinning of the nail with accelerated growth, a true hypertrophy, and I long ago attempted to unite these conditions of the nail plate, which only reflect the mechanical conditions of their surroundings, the "nail follicle," under the term: deformities of the nail, and to remove them completely from the atrophies and hypertrophies of the nails.

Simple hypertrophy of the nail, so far as produced by a multiplication of the nail cells, is therefore limited to the rare cases of enlargement of the nail plate as an accompaniment of the general enlargement of the ungual phalanx. But there is further the question, whether the nail hypertrophies may not develope simply on the basis of a greater cohesion of the nail cells. This genesis of nail hypertrophy also meets at the commencement with honest doubt, for nail cells are distinguished from other horny cells by their greater coherence, and a still greater firmness of connection could not be attained without important change in the nail cells, *i.e.*, without some anomaly of cornification. As a fact, we only see this form of hypertrophy of the nail, where the nail substance presents the hardness of tortoise-shell, ox-horn, or some such horny substance, and the histological characters of the normal nail cell are gone. But this is no simple enlargement of the nail; it is a Keratoma of the nail substance.

These cases are in no way primary changes of the nail, but are secondary to keratoma of the nail bed; they are cases of Onychogryphosis, which we may now consider, it being sufficiently clear that they in no way correspond to the definition of a simple primary hypertrophy of the nail.

The knowledge of Onychogryphosis we owe entirely to a small but valuable work, published by Virchow in 1855, in which the etiology, definition, clinical division and histological explanation of the affection are all given in complete, classical order. The years which have gone have brought nothing fresh, and unfortunately—as the reading of the

* Of course I only mean those thinnings and thickenings of the nail plate, which appear as the mechanical results of the alterations of the cutis in these skin diseases. For the changes which are induced by the affections of the matrix and the nail plate, see under Onychoses parasitariæ and Atrophy of the nail.

section Onychogryphosis, in certain new text-books, *e.g.*, in Ziemssen's, shows—some have either forgotten what was known, or not understood it. To many experts this valuable piece of dermatological literature appears to be quite unknown; therefore I cannot refrain from largely quoting Virchow verbatim, and the more, as my own investigations in all the main points only confirm his.

With Virchow, we can distinguish three forms of gryphotic nail: the *plate*-shaped, the *conical*-shaped, and the *claw*-shaped. They represent in this order more serious degrees of one and the same affection, which, as the more recent observations have shown, are produced by the pressure of the shoe on the ball of the toe, especially of the big toe. Virchow says: "External pressure is evidently one of the most important causes of the alteration in shape of the nail plate,* which is first shortened, then pushed together and enfolded, or better, padded"—and "the best proof of the connection (of the different forms) lies in the fact that all of them may be found on the toes of the same individual." Here we have only to add that, as in the development of corn and ingrowing nail, once the changes are developed, no further pressure is necessary to maintain the affection. Thus we find the best examples of gryphotic nails, in old people who have been bedridden, and their claw-like nails can, on account of their excessive hardness, neither be cut nor inserted into an ordinary shoe.

Virchow found, in all cases, the important primary change to be a shortening, often a diminution of the nail bed, usually accompanied by a dilatation of the posterior nail fold. The pulp of the toe is always less than normal; from the anterior border of the nail, the skin of the toe descends abruptly. In the slightest degree of compression of the nail bed, this has a trough-shaped, deepened form, and is thus removed from the under side of the nail plate. At the same time the subungual blood vessels dilate. Either owing to this, or simply as a result of the removal of the pressure of the nail plate, the prickle layer of the nail bed proliferates, and produces, on the one hand, an abnormally high system of narrow ridges, and, on the other, an ever-increasing cushion of horny layer. This elevates the nail plate from the nail bed, especially at the anterior angle, the elevation diminishing towards the region

* It is not to be denied, that Onychogryphosis is sometimes very marked in Tabes and in chronic nerve diseases generally (Myelitis, peripheral nerve paralysis). Wölfer has observed Onychogryphosis of all the finger nails, in atrophy of the skin following fracture of an arm (Pseudo-sclerodermia). A direct nerve influence is not necessary. In some of my cases the Onychogryphosis was accompanied by a general atrophy of the skin, which, just like pressure from before backwards, had led, by centripetal tension, to the same shortening of the nail bed, and an exposure of the posterior fold. Such a genesis may also have been present in Wölfer's case of "Sclerodermia." Then we must consider, that, whenever the gryphotic change has commenced, the years in bed which those nervous cases, as well as old bedridden people spend, very much favour the undisturbed development of the gryphotic nail.

of the lunula, never quite reaching it. The subungual horny layer in the neighbourhood of the anterior border, has always the character of ordinary horny layer, with a well-developed granular and basal layer, and looks as if the horny layer of the finger pulp had extended under the nail. Towards the lunula, the granular layer is often absent, evidently because the pressure of the nail is here greater. Here are found the epithelial depressions described by Virchow in the cutis of the nail bed, and also the foci of degeneration which he observed in the horny layer, which, in the thicker forms of Onychogryphosis, regularly lead to the formation of a sort of medullary substance. The former were first observed by Rainey, who regarded them as follicles. Virchow recognised them to be processes of the normal or pathologically altered nail-bed epithelium, and as accidental formations, with no special significance. He distinguished three forms: small cylindrical, larger bottle-shaped, and round concentric ones. Only the latter are completely snared off from the epithelium of the nail bed, and contain horny pearls. I too have found these different forms in abundance, irregularly distributed in different gryphotic nails. The medullary formations inside the horny layer are, as everywhere, due to the existence of some especially high papillæ, and are seated exactly over their apices. I postpone their description to the severer forms of gryphosis, in which they are more fully developed.

The nail plate, in this slightest degree of keratosis, suffers little, but the later affections are commencing to develope. It still has its plate form, but is thickened, and, especially on the surface, covered with cross ridges, overlapping backwards. Further, its consistence is distinctly increased, and its colour yellower and darker. The posterior fold is also almost always widely open, and filled with a thicker horny scale (remainder of the eponychium) than normal. On longitudinal sections of the nail, we see that the external changes correspond to microscopic changes of the nail plate. The individual horizontal nail layers are shortened, and do not cover each other to such an extent as in the normal nail plate. Then they contain fewer air bubbles—black by reflected light—and the nuclei of the nail cells disappear in streaks. The cut surface is therefore much more homogeneous than that of the normal nail. Finally, a terracing is evident in it, especially marked in the higher forms. This is shown at the posterior angle of the section, in a sudden change of direction; the posterior contour of the nail first rises pretty abruptly, then suddenly turns horizontally, then again rises, and so on. This intermittent prominence of thick lamellæ of nail substance appears on the surface of the nail plate as simple cross folding. Virchow says: "the increased cross folding can only be explained by an intermittent increase of formation; it points, like

the white lines described by Reil and Beau, to a series of recurring disturbances." It seems to me that this intermittent advance of the nail layer is only to be explained by the fact, that the nail finds considerable resistance in the newly developed horny layer of the nail bed, over which it must pass. At a given moment this is so great, that the nail layers are compelled to ascend more abruptly. Thus the nail plate becomes thicker, the nail opposes more resistance to the horny layer of the nail bed, and, after a time, this resistance is so great, that the advance of the next nail layer can now take place forwards, until a new balance is reached. Then the advance again ceases, the abrupt elevation again begins, and so on. Enough, I find the recurring disturbance of Virchow, not so much in the formation itself, as in the restraining growth of the competing horny layer of the nail bed, which intermittently prevents the advance of the nail.

With increased pressure on the pulp of the toe from before, the nail bed deepens still more, and, at the same time, pushes together its posterior part, in front of the lunula, into a considerable swelling, which, on longitudinal section of the nail, forms a pointed crest, several millimetres high. The nail plate is now an almost perpendicular horny cone, and is covered in front with layers of soft, leafy, horny masses, which are elevated almost perpendicularly over the shortened nail bed, and are concealed from view, above and laterally, in the excavation of the shield-like nail plate. The posterior fold lies wide open, and forms a flat groove, from which the nail plate abruptly rises. The sunken cover of the posterior fold forms, like the nail bed, a thick, ordinary horny cushion. If we remove this whole conical gryphotic structure from its basis, we see two incompletely separated grooves running across the ungual phalanx, of which the anterior represents the nail bed, the posterior the posterior nail fold. Between them is a wall, conical on section, indenting the lunula, so that, instead of being round, this has now a biscuit shape. Thus the nail plate is rooted, not only in the posterior groove, whose anterior part it completely fills, but also on the posterior sloping edges of the wall, which rises from the cutis. Thus the whole height of the wall, its anterior sloping sides, and the greater part of the anterior groove, form the matrix for the horny substance of the nail bed. The two horny parts of the cone are, on longitudinal sections, as distinct as possible. We have behind, the homogeneous, dark yellow, translucent, very hard, terraced, almost perpendicular nail, ascending forwards in a gentle curve, and in front, the much broader, greyish yellow, completely opaque, relatively soft horny layer of the nail

bed, arranged in perpendicular layers corresponding to the folds, which extend downwards from the nail plate, as the beard of a whale hangs from its upper jaw.

Even microscopically, as Virchow noted, the margin between the nail plate and the horny layer of the nail bed is very sharp. In neither horny substance do any nuclei persist, but in the substance of the nail plate there is no indication of cell margins, while in the looser horny layer of the nail bed, except in the under layer, they are distinctly evident. Thus the staining distinctions are evident with the simplest stains (picro-carmin, hæmatoxylin); they are distinguished, as usual, the firmer from the looser horny layer (yellow and red, white and bluish); these differences in colour may be seen with a higher power to extend to the closely-packed cells at the junction of the layers. Both are distinct from the corresponding layers of the first grade of Onychogryphosis.

The nail plate has become completely a-nuclear, darker yellow in colour, very dense and hard, and the terracing is much more distinct. In the larger gryphotic cones, which reach the height of one to one and a half inches, there is seen a marked increase in breadth in the terraces. While the steps near the apex are about 1 millimetre broad, and consequently closely arranged, those at the base of the cone have a breadth of 4-5 millimetres. As described above, this increase in breadth indicates a resistance of the nail plate, increasing with the age of the gryphotic structure, which is readily explained by the constant increase of its consistence. In all these characters, especially the loss of nuclei and the hardness, the gryphotic nail plate differs so much from the healthy, that it can hardly be described as simply hypertrophic. It represents a particular form of Keratoma of the nail matrix, just as the horny layer of the nail bed is a Keratoma of that.

In the latter, compared with the first stage, there are further changes. The wall which developes at the most posterior parts of the nail bed, has led to a separation of the heaped-up horny layer into two parts, a firmer portion over the wall, and a looser one over the anterior groove. The vascular wall acts on the horny layer over it, like a giant papilla. The horny layer is arranged in dense, arched layers above the wall, and shows the same swelling and softening of some horny cells as occurs over the papillæ in cutaneous horns, and is there described. But here, this softening of the horny substance, corresponding to the breadth of the wall, is more extensive, and leads to the formation of very broad medullary spaces and columns. Inside them, as Virchow noted, the softened cells often run together to form large cell complexes, and medullary spaces of considerable size. In the lowest of these spaces, there is often complete liquefaction and absorption of the

cellular contents, and with an appropriate stain, we can often see in them a net of thready fibrin. We frequently find hæmorrhages and deposits of blood pigment in the medullary spaces, mechanically induced, as in cutaneous horns; these also were fully described by Virchow.

In the anterior part of the horny layer of the nail bed, there are less distinct changes. The prickle layer shows, in addition to the persistent ridges, an abundant proliferation of irregular epithelial taps, a pretty high supra-papillary layer, then a very small granular layer, and a broad basal horny layer. In many places the granular layer is altogether absent, as it is above the wall. Nevertheless the basal horny layer contains no nuclei, nor do these again appear in the heaped-up, loose horny layer, of which the anterior horny part of the gryphotic cone consists. We have therefore to do with an anomaly of cornification, and not with the simple over-growth of the nail bed by the normal horny layer of the pulp of the toe.

The third stage, of *claw-like* nails, is simply an extension of the same change which induces the first and second stages. The pressure leads to an almost complete disappearance of the nail bed, the anterior groove being distinctly smaller, and the wall between the two grooves —though not so much—widened. The posterior groove also becomes smaller, and thus aids in the enlargement of the wall. In the second stage, both grooves were flat and opened anteriorly, in the third they are both deeper and open directly upwards. The wall, which was previously inclined forwards, and was somewhat pointed, now rises perpendicularly, and has become so broad, that it forms, almost alone, the basis of the gryphotic structure. As it attacks the region of the lunula from the front, this alters its biscuit form into a half-moon. So, simply by constant pressure and the compression of the tissue from in front, the matrix of the nail plate, or rather the matrix of the nail keratoma, is converted from a round surface into a half-moon, which surrounds the middle wall and extends to its posterior surface. This completely explains why the nails, which show the highest degree of gryphosis, have a semi-lunar bent section, and are much flatter than the conical form of the second stage. More precisely, the development is the following. The conical nails are first flattened from before backwards, then, by the loss of a further part of the nail bed, part of the anterior, loose horny layer falls out. Thus the horny layer of the nail bed is soon reduced simply to that firmer part, which is seated on the summit and the anterior part of the wall, and shows the medullary formation described. This, together with the keratoma of the nail plate, now forms a hollow horny cone, which sits like a pointed cap on the central wall, and surrounds it, behind and at the sides, as a com-

pletely homogeneous sheath, in front, as a loose mass. From the thick solid cone of the second period, there is developed, by the advance of the central wall (the cutis fold) and diminution of the nail bed, a distinctly flatter and more excavated, cap-like horny structure. I have a whole series of such pointed horny caps from one foot, which were easily and completely removed from the different toes, and are all formed as if over one ridge.

From these pointed and flat hollow cones, we can see all stages of development, up to the longest, most extraordinary claws. Since this hollow sphere advances from beneath, and thus maintains its flattened form, we see in it, as in all flat horny structures—*e.g.*, the oval hairs of the beard, of the nigger, and of the sheep—the tendency to form circles or spirals. Since the extension on one side of the keratoma is greater than on the opposite side, or the resistance—here the boot—less, there is a tendency to turn to one side. So long as the whole structure is solid and mainly round, this is hardly noticeable. But there only needs to be some such slight constant influence on the flat hollow cone, and the direction of the apex alters. When this is supplied, the advancing structure necessarily follows the same direction. So there develope claws, which bend downwards, grow round the pulp of the toe, and therefore appear at the first glance to consist only of nail substance; claws, which are bent backwards, gradually bore into the dorsum of the ungual phalanx, and show, on their surface, a central streak of nail bed horny layer; and, finally, claws of all sorts of spiral form, like the horns of rams and antelopes. If the pressure and the atrophy of the pulp of the toe and of the nail bed persist, these claws, after years of development, show the change by becoming smaller and hollower towards the base. Finally, after years of existence, the horny layer of the nail bed falls completely out, and the gryphotic nail is now formed simply of altered nail plate, which, like a half tube surrounding the central nail swelling, springs from the stumpy, shortened ungual phalanx. In this way, the terminal stage of Onychogryphosis approaches certain atrophies of the nails, in which mainly the nail bed atrophies (see atrophies of the nail).

The third or claw stage is therefore, although the nail is much longer than in the second, to be regarded rather as a retrogressive stage. This is a point in which my observations do not exactly agree with Virchow's; according to him, the claw form should be placed between the first and second stage. I regard it as the highest and ultimate manifestation of the gryphotic process. The same pressure from before, which in the first stage only elevates and condenses the nail plate, leads in the second to a contest between the condensed nail and the actively growing horny layer of the nail bed, and at last over-

comes the latter, so that only the nail plate, much altered in form and consistence, remains. I believe that in this my view is more uniform than that of Virchow, since it regards all the forms as different stages of the same mechanical action.

And I also differ, though unimportantly, from Virchow, in regarding the process as non-inflammatory, while Virchow is inclined, like Rayer, to regard it as a chronic inflammation of the nail. It is indeed very questionable, whether there are any purely mechanical inflammations,* and Onychogryphosis must be such an one, for it is induced purely mechanically; in this I fully agree with Virchow. The dilatation of the blood vessels in the compressed nail bed I also regard as purely mechanical, and the hyperæmia as the sign of stagnation, not of inflammation. Were a chronic inflammation of the cutis really the cause of the nail deformity, there would be signs of it in every case, *e.g.*, enlargement and multiplication of the connective tissue cells around the vessels. But I found this only exceptionally, and its occasional occurrence in structures so exposed to injury as onychogryphotic nails, is only to be expected.

But as a whole, this description is based entirely on that of Virchow, and I will conclude with a very few valuable statements of our old master, which still possess all their value, for there are still authors who would reserve to the nail bed a share, "though only limited," in the formation of the nail. Virchow says: "At the first glance it is evident, that this peculiar formation is mainly due to the fact, that the two sections of the nail base, the anterior and the posterior, or the nail bed proper and the matrix, form different substances, the nail which advances along the matrix remaining relatively normal, while the (anterior) nail bed produces the scaly mass. In regard to nail formation in general, this is a most interesting observation, for it shows to what a degree the nail is formed independently † from the fold and the lunula." And: "For the physiology of nail growth, the experience is of importance, that even in the claw-like degenerations, where only the leafy lower layers are evidently formed from the nail bed, the nail bed is not only completely present, but may even increase in thickness from before backwards. In such a nail, from the big toe, I measured the thickness of the nail body a quarter of an inch larger than that of the nail root. The reason for this increasing thickness lies, not in the formation of new nail substance from the nail bed, but rather in the addition of constantly renewed slanting layers on the matrix. The nail bed proper consists, not of layers which are completely parallel to the surface; they

* See traumatic inflammations of mechanical origin.

† Independently of the nail bed.

rather lie with the anterior ends of the posterior layers, under the posterior and middle parts of the anterior layers. At the root, where the number of layers is less, and finally only a simple layer remains, the nail must therefore be thinnest. It appears to me that, as Reichert has stated, in the normal circumstances nothing is produced from the nail bed but a sort of cushion, on which the nail advances; the leafy character of the masses which appear under the free border, corresponds to the leafy arrangement, which the thick substance beneath the elevated nail bed in gryphotic nails shows."

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(b). *Cysts.*

(aa). *Traumatic epidermic cysts.*

These appear in adults, especially those (locksmiths, masons, seamstresses) whose calling exposes them to blows or pricks with instruments, on the volar sides of the hands and fingers, in the form of round, indolent, movable tumours, usually about the size of a pea, whose development can usually be referred to some trauma. Kummer and Christiani found the point of a nail in such a cyst.

This interesting form of tumour forms a spontaneous contrast to the "artificial atheromata" in the well-known researches of Schweninger and Kaufmann. They have been thoroughly investigated by Audry and Lacroix. In the case of a young girl, who had pricked herself on the thumb with a needle, there developed an epidermic cyst the size of a pin head, which was surrounded by a connective tissue membrane, without either papillæ or vessels. The prickle layer of the epithelial core of the growth consisted of flattened cells, which showed nuclei, but no prickles. A layer of two to five rows, containing some diffuse elëidin, formed the transition to the a-nuclear horny layer, consisting of lamellæ taking up carmin, and in the centre passing into an uncornified debris. In this case the deep epithelial layer turned back on itself, and thus formed an enclosed sphere. The conditions were very different in a second case, of an almond-sized tumour in the thenar skin. Here the epithelial mass could be separated into two distinct layers, a thin germinal layer, consisting of six or seven rows of prickle cells, in which no kerato-hyalin was recognisable, and a very

much broader, leafy mass of carmin-stained, incompletely cornified, older epithelia, showing plaques of elëidin. The connective tissue next the outer layer was dense, a-vascular, and poor in cells, the germinal layer was surrounded by a less dense collagenous tissue, in whose spaces lay, sometimes a-morphous blocks of epithelial origin, sometimes masses of altered blood corpuscles, and sometimes large cells with numerous nuclei, which are regarded by the author as wandering cells, destined to promote the resorption of the degenerated epithelia. But they should rather be regarded as chorio-plaques or giant cells.

From these observations it is clear, that epidermis accidentally brought into the depths of the skin remains capable of reproduction, but no longer forms kerato-hyalin, that true surface cornification takes place, and that, further, it is of importance in encapsulation, whether the implanted germ can round itself off; this probably depends on its absolute size. A true enlarging cyst can naturally only form in connection with those germs which take the spherical form, and are nourished, though sparsely, on all sides. The formation of an absorbing granulation tissue, in place of the encapsuling connective tissue membrane, makes the development of a cyst impossible, in spite of continued epithelial formation.

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(bb). *Follicular Cysts.*

The most recent worker on follicular cysts, H. Chiari, who had before him a large series of so-called false Atheromata, distinguishes sebaceous cysts from cysts of the hair follicles, and thus tends to confirm the widespread view, according to which there are sebaceous cysts and hair follicle cysts in the proper sense of the word. Now it is clear, even from this excellent work, that the lobules of the sebaceous gland never share in the cystic formation, and that the cyst always affects only their exits; in other words, a cyst of the gland itself does not exist. This corresponds exactly with my experience, and I have repeatedly noted in this book, that wherever pressure, due to growth or secretion, acts backwards on the glandular cells, these undergo atrophy,

and are converted into a layer of ordinary epithelium. But this general principle is not limited to the secreting surface of the sebaceous gland; it extends also to the germ of the hair. So long as the cystic dilatation has only affected the region from the mouth to the under third of the hair follicle, the proliferation of the hair does not suffer, and the casting of the hair goes on perfectly, if the under third be not compressed by the cyst. But if the dilatation reach the bottom of the hair follicle, the growth of the hair at once ceases; a cyst of the hair follicle in the proper sense, which comprises the whole hair follicle and still produces hairs, does not exist. It may therefore serve as a general law, that where sebaceous gland and hair is preserved, it is only a cyst of the duct; this appearance is still more distinct in the coil glands. It would consequently be logical to distinguish five varieties of cysts of the follicle: (1) those of the follicle exit with retention of the hair; (2) of the sebaceous gland exit with preservation of the gland, and then, after disappearance of the specific epithelia, those, (3) of the hair follicle, (4) of the gland, and (5) of the whole follicle. But practically, the last three forms fall together, for isolated cysts of the gland do not exist, if we understand by that, cysts which occur in the same follicle with preserved hairs. Nor are there isolated hair follicle cysts, with well-preserved sebaceous glands. If there is complete arrest of the specific function of one of the two germinal layers, the distension of the follicle walls and the internal pressure are so great that both disappear; we have a simple follicular cyst. Thus the possible varieties of follicular cysts are reduced to three.

But we have next to consider that cysts of the sebaceous outlets, as a fact, unite with those of the hair follicle exit. Chiari certainly describes isolated cysts of the exit of the gland, which contain at the commencement an excess of sebum, and later, horny masses, and are distinguished from the cysts of the outlet of the hair follicle by their minuteness and their limitation to the cutis. I, on the contrary, have, neither in the isolated larger cysts, nor in the abundant material which the study of Acne, Ichthyosis, Pityriasis rubra pilaris, Keratosis follicularis, Favus and Lichen has supplied, ever observed an isolated cyst of the outlet of the sebaceous glands. They are always in the common outlet of hair and sebaceous gland. Of course if, on those parts of the skin which have large sebaceous glands and small lanugo hairs, one ignores the latter, one may speak of isolated cystic formation of the outlet of the sebaceous glands; but this want of accuracy has no practical advantage. For the rapid comprehension of the matter, it is much less important to know whether the formation of cysts of the common duct is more correctly to be ascribed to the hair or to the sebaceous glands, than to know the *contents and the position of the*

mature cyst. This depends on two circumstances: on the extension of the cystic process, and on the integrity of the hair-root and the epithelium of the sebaceous gland; both conditions are mutually interdependent, since with increasing extension of the cyst, the formation of hair and sebum suffers equally or in different degree.

I therefore regard it as more correct, and corresponding more to the actual differences, to regard the follicular cysts as a uniform group, and divide them, according to their contents, into horny cysts and sebaceous cysts. In the name horny cyst, we indicate that the production of sebum has completely or largely ceased, that, in other words, the sebaceous gland is destroyed, while the word sebaceous cyst directly points to the integrity of the sebaceous gland, or a part of it. A hair cyst, as a third form, would be logical, but is practically unnecessary, because, on the one hand, even if the hair matrix is preserved, the casting of the hair may be arrested, and, as a fact, is so often arrested that cysts with many hairs are rare, and, on the other hand, those cysts which contain numerous hairs and are macroscopically visible almost always contain a large amount of sebum, and may therefore be named sebaceous cysts. One might rather speak of *mixed follicular cysts*, where horny substance and sebum are produced in equal amount, as in many comedones.

The horny cysts form by far the larger and more important group, not only because the cystic process converts the follicle, the more it extends, the more completely into a surface which produces horny substance, but rather that the formation of most cysts is introduced by a hyperkeratosis, which extends from the mouth of the follicle, so that the horny contents consist, not of the accumulation of normal epidermis, but of the products of a morbid, abnormally abundant horny layer. The most characteristic horny cysts depend on a hyperkeratosis of the follicular exit.

The sebaceous cysts are much rarer, simply for the reason, that a hyperkeratosis of the follicle mouth, which closes them and does not extend into the follicle, is rare; usually the excessive amount of horn leads to a horny cyst, or at least to a mixed one. Now and again, sebaceous cysts develope from mixed cysts, if the horny production gradually ceases, while the production of sebum continues. Many sebaceous cysts contain more or less hair.

(aaa). *Horny Cysts.*

The horny cysts are either microscopic, externally invisible follicular cavities, filled with horn and sometimes concealed beneath scales, or they appear in the form of pearly white, shining, non-expressible granules, which

shine through the epidermis, or project it semi-spherically. In other cases they appear as black points and distensions of the follicle mouths, from which lateral pressure discharges a horny body, blackened at the head (so-called black-heads). This latter form of cyst may assume very considerable dimensions, and open on the surface with several openings and black-heads.

1. *Small cylindrical horny Cysts; Comedo, Double comedo.*

The most varied pathological processes give origin to cylindrical horny cysts of the exit of the follicle, which we call Comedo. Common to all of them are the following characters. They have a long, cylindrical or ovate form, are somewhat darker at the upper end, yellowish-brown to black (usually about 3-4 millimetres long, 1-2 millimetres broad), and are easily separated, as independent structures, from the younger horny layer of the follicle neck. They vary according to their origin, for they are almost all secondary products of the different affections in which they are present.

The commonest form is that in Acne. Here, in most cases, we have, not a pure horny cyst, but a mixed cyst, for Acne punctata never leads to destruction of the sebaceous glands. There is hardly any form of cyst in which horn and sebum so regularly share in the formation of the contents. The ordinary form of the acne comedo is that of an acorn or a lemonade bottle, in which the neck represents the blackened head of the comedo. Inside, separated by horny septa, lies the compressed sebum. Where the production of sebum is slight, the comedo is horny down to its lower end; where it is greater, it terminates in fat. The acne comedo is distinguished from other comedones, on the one hand by the regular presence of sebum, on the other by the presence of Acne bacilli. In doubtful cases, the latter alone is conclusive.

Acne pustulosa often leads, by suppuration of several adjacent follicles, to the formation of double, triple, etc., comedones. These were first described by Ohmann-Dumesnil, and more closely by v. Düring. The latter attributes their development to the confluence of several hair follicles inside the skin, an occurrence, whose existence had been confirmed by Török in Acne pustulosa. Since in Acne the sebaceous membrane long resists complete suppuration, but is greatly distended, an intra-cutaneous adhesion with neighbouring follicles, which are also suppurating, is as easily possible as the union of the walls of one and the same follicle. In healing, there developes in the first case a common, barrel-shaped cavity, close under the surface of the skin, which, according to the number of the suppurated and adherent follicles, has two, three or more openings on the surface, and usually as many remains of hair follicles and sebaceous glands underneath. This is closed by simple

flat epithelium, and produces horny substance, which fills the cavity in concentric layers, and sends blackened and compressed processes towards the different orifices. In very old double comedones, the blackening sometimes extends to the middle of the bag-pipe-shaped cavity. The remains of the hair follicles consist, either of short,

FIG. 32.

Suppuration of two adjacent follicles *b*, *b*; *a*, *a*, the remnants of the sebaceous glands are seen; the central cavity filled with pus and debris of tissue.

well-preserved follicles, which, from time to time, send small lanugo hairs into the cavity, or of remains of sebaceous glands, which, usually compressed by the cyst, have taken a flat form, and sometimes surround a great part of the cyst in this atrophic condition. They also contribute, by the separation of sebum, to the contents of the cavity, and I once found such a gland opening into the common cavity by a long, thin, cork-screw-like duct. Usually the remains of

the original follicle are, by the diminution of the cavity during scarring, drawn out, first in a radial direction ; in the later enlargement and distension of the cavity, they are placed more horizontally, the orifices being pushed downwards.

FIG. 33.—Double Comedo showing ultimate stage of last figure.

a, *a*, Persisting remnants of hair follicles and sebaceous glands. The double comedo stretches from the one opening to the other, and the blackening is seen to run all through, quite independent of external conditions.

There arises the not unimportant question, whether the double comedones are kept up by a dormant acne process, or whether, after the skin has been thus deformed by scarring, this is sufficient to keep up the formation of comedones ? In this connection I have examined a double comedo, and found it filled, not with acne bacilli but with a pure culture of the bottle bacillus. This one observation proves that the persistence of the double comedo is not bound up with the existence of acne bacilli, but it does not decide the question whether the deformity of the skin is sufficient.

The black-heads most like those of Acne, are found, along with spherical horny pearls, in *Keratosis follicularis circumscripta* and *Keratosis follicularis contagiosa* Brooke. The comedo-like products develope in cylindrical or conical distensions of the upper two-thirds of the hair follicle, the horny pearls in the completely destroyed and distended follicles. From the acne comedo, they are mainly distinguished by the fact, that they are pure horny cysts, and therefore contain no fat. The process of cornification in the exit is so great, that the comedones are completely horny, and thus the entrance of the

fat from the *well-preserved, non-hypertrophic, non-cystic* gland beneath into the comedo is prevented. These comedones are distinguished by the regular lamellar arrangement of the horny lamellæ, and the rarity of enclosed hairs.

In Ichthyosis, also, we meet, under the scales, with very dry, comedo-containing horny cysts. In these hair follicles, the sebaceous glands are also usually atrophic. They contain—corresponding to the duration of the disease—usually several lanugo hairs, which are irregularly arranged between the horny lamellæ. Thus the whole formation of the comedo is irregularly septate. By their containing hair, and by the absence of sebum and distinct blackening of the upper end of the comedo, as well as by the absence of Acne bacilli, the comedones of Ichthyosis are clearly distinct from those of Acne.

Widely extended are the *scar comedones.* We commonly, and no doubt rightly, ascribe to simple mechanical conditions the cystic degeneration of the hair follicles in scars, and especially in the border of scars next the healthy skin. As a fact, the retraction of the scar, by giving to the neighbouring follicles an oblique direction, often enough narrows or closes the follicle mouth. Then comes a factor in the scar, which, as in Acne, favours the hyperkeratosis; viz., the anæmia of the skin, especially of the papillary body. The delayed metamorphosis leads to slower casting off of the dry horny layer. I believe that both factors—narrowing of the follicle mouths and hyperkeratosis from anæmia—must combine, in order to produce comedones in scars, for on permanently hyperæmic scars no comedones develope.* The scar comedones resemble very much, in form, in the amount of fat, and in their black head, the acne comedones, but are distinguished from them by the absence of Acne bacilli.

The scar comedones may also form double, triple, and multiple comedones, for, in the union of a cut surface, the halves of neighbouring follicles may, by contraction, be brought close together, and unite intracutaneously. Then one can sometimes push the comedo from one side with a probe, the probe going under the middle of the scar. In healing by second intention, several follicles may grow together to form multiple comedones. One might be inclined, since the double comedones of Acne appear only secondary to processes of ulceration in the follicle, to indicate all double comedones as scar comedones, and if it should be, that, even in the double comedones of acne, the Acne bacillus is never found, this view would be justified. In scar comedones, which do not arise from acne scars, I have as yet never observed the Acne bacillus, or micro-organisms in general. These scar comedones sometimes show an extraordinary length, if they arise from canal-formed, horizontal

* So-called milia, *i.e.*, sebaceous cysts, do.

horny cysts. They pass on both sides into black-heads, and one can, in old specimens, *e.g.*, of scars of the groin, sometimes follow the blackening through the whole canal, which alone contradicts the idea that the blackening of these comedones is due to dirt (conf. Acne). Large horny cysts sometimes develope from these double comedones.

All follicular cysts of cylindrical form, which develope by a marked dilatation of the upper two-thirds of the follicle, or of a smaller area, and contain comedo-like horny plugs, pass underneath into a remnant of the hair follicle, to which is often added a sebaceous gland. The behaviour of these glands, where they are preserved, is instructive, and throws some light on their function in other processes. They do not necessarily atrophy, where the upper part of the follicle—as, for example, in Ichthyosis, Hyperkeratosis supra-follicularis—is completely blocked by an entirely horny plug; nor do they show, in these cases, a hypertrophy, which one might expect to see in view of the continued production of sebaceous cells. Finally, there never developes in such cases, a sebaceous cyst underneath the horny cyst, inside the remains of the sebaceous gland. We have therefore sometimes a gradual atrophy of the sebaceous glands, down to the simple type of prickle layer, or the preservation of a status quo, which is still more remarkable. Indistinct as these symptoms may appear, they are not, as we would expect, simple appearances of retention. If we compare the behaviour of these sebaceous glands with a cystic alteration of the exit, in which mixed comedones, containing sebum and horn, develope as in Acne, we find the gland functionally active, and a true stagnation of secretion, first in the common, then in the special glandular duct, and finally in the lobules of the gland itself; but there is never a regular cystic formation in the gland. Instead of the glandular epithelium being re-converted into prickle layer, the last trace of germinal layer is converted into sebaceous cells. This is a remarkable difference in the behaviour of the same gland under the same external conditions of closure of the follicle. To me it appears that we cannot avoid assuming chemotactic, and especially sebotactic influences. It seems to me possible that the fat-loving and fat-consuming Acne bacilli, in spite of the closure of the follicle and the high pressure, induce the production of new masses of sebum.

The points of comparison with the forms of seborrhœic catarrh are evident from the same standpoint, and do not need further notice.

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2. *Small spherical horny cysts.—Horny pearls.—Milium.*

The horny pearls developing in spherical horny cysts vary much in size and in position in the follicle, and differ from one another much more than the regular-sized comedones, which are always seated in the upper part of the follicle. Further, they never contain fat, and are not dark at one end. The smallest are found in the follicle neck, the medium ones in the centre, and the largest ones in completely destroyed, distended follicles. In the latter, the size varies with the size of the follicle; it is therefore in general less in cystic transformation of the follicle shortened by the hair casting, and in the lanugo follicle.

Very small horny pearls are found in the spherical follicle necks in *Pityriasis rubra pilaris*, more rarely in *Lichen*. They are hardly visible with the naked eye. They contain at most one or two hairs; usually they consist of concentric horny lamellæ. While these horny cysts develope by extension of the hyperkeratosis to the follicle infundibulum, in *Hyperkeratosis supra-follicularis* (so-called Lichen pilaris) small cysts develope in the follicle neck by simple stagnation. This is to be ascribed to the closure of the follicle by the purely supra-follicular hyperkeratosis. The result is that here no very firm, concentrically-arranged, pearly, horny bodies develope. Between the loose horny collections we always find a spiral hair (rarely several), and the steepness of this spiral is to be ascribed rather to the cystic distension than to the pressure of the stagnating horny mass. The sebaceous glands, which may either be preserved or atrophic, do not contribute by their products to the enlargement of the cyst.

Larger horny pearls as well as comedones are formed in the ordinary *Keratosis follicularis contagiosa* Brooke, when the whole follicle is converted into a horny cyst. The latter is then spherical or oval, and rarely reaches beyond the middle of the cutis downwards. Almost always, we note, in the under half of the wall of the cyst, minimal remains of the follicle base, in the form of epithelial processes, and usually also a sort of protuberance, which, by the preservation of a few sebaceous cells, is recognised as the remains of the sebaceous gland. The cysts are almost always "anchored" by a somewhat cellular connective tissue cord, extending downwards: the old follicle. New epithelial growths are rarely found around these cysts, or at least are difficult to recognise as such, for, in view of the chronic formation, we see no mitoses. Most of the small epithelial growths appear to be remains of old outgrowths of the follicle epithelium, which are normally present, and which are not completely obliterated in the distension of the follicle.

There is, further, an affection in which the size of the follicular

horny cysts so contrasts with the minuteness of the affected follicles, and where the affected region of the skin is so delicate and yielding, that the horny cysts project distinctly over the surface of the skin, and are visible as pearly white, shining nodules. On account of the miliary size of most of the cysts, this affection is called Milium.

Milium.

Miliary, spherical, bluish-white, shining, hard, superficial granules, without recognisable openings, which appear in groups, frequently on the face, very rarely on the genitals, persist long at a certain size, and later spontaneously disappear. Their seat of predilection is the region of the zygoma and under eyelid, then the forehead, nose, lips, and the rest of the cheek. Where they are numerous, some of them reach the size of a peppercorn ; yellowish tumours the size of peas, dotted with black points and seated deep in the skin, are not milium, but are other forms of retention cysts, usually sebaceous cysts. It is doubtful whether the milium-looking bodies, which appear in groups in the healing of Pemphigus, Tertiary syphilis, and on scars, as well as most milia of the genitals, are to be regarded as true milia. They form more rapidly and are more rapidly exfoliated than the typical milium of the face. The so-called milia of infants are sebaceous cysts.

Virchow, who first thoroughly investigated the condition, correctly ascribed it to the accumulation of an excessive number of horny cells in the deeper parts of the very short lanugo hair follicles, such as are present on the predilection seats of Milium. The horny layers are—in contrast to comedo—arranged like the scales of an onion round a point which is often eccentric. " This form is so far of special interest, that it has a structure like a pearl, and, by the heaping up of individual layers, a true pearly appearance often developes, viz., that rough, silver-like shine which distinguishes the true pearl " (Vol. I., p. 219). In addition to the horny mass, Virchow further found a greater or less amount of fat, and attributed the great differences in its amount mainly to the level at which it developed in the hair follicle, and the relation of the sebaceous gland to the latter. They may be perfectly free from fat, deep down in long hair follicles; in small hair follicles with large sebaceous glands, the fat is in abundance, in the form of sebaceous cells, free sebum, and plates of cholestearin. This latter statement probably does not refer to milium, for, in the description, Comedo and Milium are reckoned together. But Virchow specially notes in Milium the presence of acicular cholestearin crystals.

Later investigators mostly reproduce these statements. Rindfleisch regards all milia as deep cysts of the hair follicle ; according to Neumann, Milium lies either in the hair follicle or in the sebaceous gland, for its follicle consists " of the thickened wall of the hair follicle

or the sebaceous gland," from which, " in the larger lobulated growths, numerous connective tissue septa extend." This shows, as does the drawing (Fig. 12), that Neumann was examining, not Milium, but a large sebaceous cyst; connective tissue septa have not been found by Virchow and Rindfleisch or by any one else in Milium, and the spherical, pearly, true Milia are not lobulated but have a scaly form. Robinson separates two forms of Milium, of which the one is due to an aberrant germ of the prickle layer, either from the surface or from the hair follicle, contains no fat, and shows no exit, while the other is a deep-seated comedo, containing cholestearin and sebum, and with an outlet.

As we see, sebaceous cysts and comedones have been described, under one name, along with true Milium; as usual, an insufficient clinical investigation has blurred the histological facts, where careful histological analysis should have explained indefinite clinical terms.

L. Philippson, in criticising Robinson's views, and a similar theory of Epstein's, who regards the epithelial pearls in the mouths of infants as true milia, established the view, that in them we are dealing with cornified epithelial pearls, which lie free in the cutis, show no connection with the surface epithelium, the hair follicles or the sebaceous glands, and are therefore to be derived from embryonic germs of epithelium. The so-called milia of infants and many of adults are, according to Philippson, nothing but sebum, which has stagnated at the exit of a sebaceous gland acinus or in the infundubulum, and forms a mass, more or less round, consisting of fine fat droplets, fat cells, fat crystals, and horny cells. Those sebaceous cysts, which may always be recognised by their yellowish colour, and, on careful search, their opening, should not be diagnosed as Milium.

My investigations of true Milium refer to a series of tumours, removed from different patients, and to a piece of skin with several milia, in which I could study the local relations of the cysts. All the preparations come from the zygomatic region, and from the under eyelid of cases which, by the areated appearance and persistence at the seat of predilection, permitted no doubt of the correctness of the diagnosis.

All the expressed milia showed the formation described by Virchow: pure horny concentric pearls. There was never any lobular formation, at most a slight folding at the margin. A fragment of prickle layer clung to some of them, but there was never any connective tissue. Usually one could distinguish a firmer horny core from a more loosely arranged marginal zone; in neither were fat cells or free fat found. Only very exceptionally could we find, in sections treated with osmium, a few small black bodies, in the outer layers. Micro-organisms were not present. The true milium is then only a horny cyst.

Further, my preparations gave important evidence on the seat of these horny cysts, corresponding to the clinical symptoms. They are all in connection with small lanugo hair follicles. Around every horny cyst, there are compressed remnants of such a follicle, and this is always connected, usually in its central portion, with the prickle layer of the cyst. The cyst thus developes in the central part of the hair follicle, *distending it in a vesicular manner to one side.* The position and the lateral seat of the horny cyst might lead to the idea that it had developed from the sebaceous gland, but the small sebaceous glands of the neighbouring lanugo follicles are seated deeper than the cysts, almost at the fundus of the very short follicles. The cysts enlarge, mainly laterally and upwards, push upon and compress, not only the remainder of their own hair follicle, but also the neighbouring follicles, which are bent round the cysts. The cutis shows a multiplication of the spindle cells, especially of the perithelia, and a condensation of the adjacent collagenous tissue. The first beginnings of the affection are, I believe, found in some of the follicles near the cysts, and are indicated by the appearance of a very clear, homogeneous horny layer, which distends the infundibulum.

Consequently we have apparently a hyperkeratosis of the epithelium of the hair follicles, which descends to the middle third, and here leads to a very severe unilateral distension of the small lanugo follicle with simple horny layer, the fundus remaining undisturbed. The clinical appearances of true Milium, as well as its spontaneous or artificial disappearance, are very readily explained by the fact, that it is a relatively superficial, follicular horny cyst.

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L. Philippson, The Relations between Colloid-milium, Colloid degeneration of the skin and Hydradenoma. Mon., 1890, V. XI., p. 1.

3. *Large Horny cysts.* (*Pseudo-Atheroma.*)

These cysts have the size of a pea, a nut, or even a walnut or more, are round or oval, and, according to the thickness and yielding of the subcutaneous tissue, dig into it or distend the neighbouring skin some distance round, and gradually induce atrophy. They are thus either movable or fixed. They always communicate with the surface by a distinct, often wide opening, which is closed with blackened horny layer, from which, with some force, one can express part of the contents, in the form of a sometimes shining mass of horny debris, with no odour. Now and again, in prolonged cases of Acne, these horny cysts appear multiple, but usually they are solitary, and their origin from inflammation of the follicles can sometimes be followed, where the normal course of healing has been interfered with mechanically, especially by frequent and forcible expression. In many horny cysts, in spite of the enormous size, the

hair matrix and the sebaceous gland are not yet completely obliterated, and we find in the expressed contents a mixture of fat and hairs. These mixed, not very common cysts form the transition to the pure, large sebaceous cysts. From the Atheromata, with which they are almost always confused, the large horny cysts are distinguished clinically by the primary seat of the Atheroma in the hypoderm, while the horny cysts descend from the cutis, by the predilection of the one for the hairy scalp, while the other is present on all parts of the body where follicles are present, and by the openings of the horny cysts, which are always absent in Atheroma.

The histology of the large horny cysts closely resembles that of the small ones, with comedones or horny pearls. Here also we find the follicle converted into a round or oval, only much larger cyst, which is completely filled by concentrically laminated, bent or folded horny lamella. The follicle is clothed by flattened follicle epithelium, which, towards the centre, now and again shows regular cornification, with kerato-hyalin, or, where the pressure is greater, an irregular cornification, in which the kerato-hyalin is altogether absent, or only present here and there. In the latter case, elëidin is abundantly present in the horny layer. In very large old horny cysts, we see in the centre, exactly as in the Atheromata, a greater welding, and therefore breaking down of the horny collections into a debris of cells, which sometimes encloses cholestearin. The occurrence of these porridgy contents in these old horny cysts, has led to the confusion with the Atheromata, which have quite another development. Like the latter, the follicle of the horny cyst now and again shows a papillary body, the growing horny layer producing shallow ridges. This was very well shown in a horny cyst, the size of an almond, from the eyelid of an old woman. This surrounded a very regular horny body, with no trace of fat, and represented the completely stretched bag of a follicle. The broad mouth was closed with a plug of blackened horny layer; the cyst had not been expressed for years. The pretty broad prickle layer, which clothed the cyst, only sent its ridges to one side, that of least resistance, where the cyst was surrounded by loose connective tissue. At the other side, the connective tissue formed a sort of capsule, and here the prickle layer of the cyst was flat, and there was no indication of a papillary body. If, on account of the papillary body, in spite of its exit and its isolated occurrence in the eyelid, this were reckoned with Atheromata or Dermoids, the door is opened to fallacy. For I was able, right in the centre of the compact horny body, to recognise faintly staining remains of a culture of cocci, showing no connection with the exit duct, while in all the outer layers of the horny body, and in the horny layer of the surface, no organisms were to be found. The cocci must have been taken up when the cyst was in connection with the surface, and in the years which had

elapsed had been surrounded by a thick horny shell. In another horny cyst, I found all the horny layers permeated by a small variety of coccus. As yet I have never found Acne bacilli in the large horny cysts, any more than in double comedones.

Especially in view of the frequent confusion with Atheroma, I cannot sufficiently recommend the careful bacteriological investigation of these bodies, which will in many cases lead to conclusions on the presence of acquired or congenital cystic formation, when other characters fail. So long as remains of the fundus of the hair follicle and of the sebaceous gland are still present in the horny cysts, so long as an arrector muscle is inserted in it, the diagnosis of a pseudo-atheroma is of course easy.

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(bbb). *Sebaceous cysts.*

In some cases we have miliary, white or yellowish, elastic tumours, the size of a peppercorn to a pea, semi-spherically distending the skin, with a smooth surface and no visible openings, in others, equally large or larger, more elongated, less projecting, flat tumours, the colour of the skin, extending into the hypoderm, with easily recognisable open mouths, from which slight pressure is sufficient to express a yellowish, often unpleasantly smelling mass, blackened at one end. The former appear spontaneously and isolated, on the face, the neck, the genitals, on nævi, or now and again in large quantities at once, especially on the scrotum and penis. The latter sometimes develope in numbers from a widespread persistent Acne, under direct observation. Some show, in addition to masses of fat, a convolution of hairs, which are periodically thrown off and re-formed. Many gradually calcify (false cutaneous stones). Sebaceous cysts are very often confused with Dermoids, Atheromata and Milium.

As already remarked in the chapter on horny cysts, sebaceous cysts only develope where the closure of the follicle is superficial, and hyperkeratosis does not descend into them. But in addition, an abundant or at least unaltered production of sebum is necessary to their formation; the glands must not be destroyed even in great distension of the sack. They therefore develope most easily on places (head, genitals) where the sebaceous glands play the chief rôle in the follicles. There are no thorough investigations on the structure of sebaceous cysts, and therefore we must draw a cursory picture with a few facts.

The smallest sebaceous cysts are the so-called *milium of infants*, which may cover the nose and cheeks, as a closely set, whitish, not yellowish, vesicular eruption. In one of my preparations there was

marked dilatation of the follicular exits, whose mouths were closed by a thin horny layer. These follicles pass, underneath, into a hypertrophic sebaceous gland, while the hair belonging to them—as in the neighbouring normal follicles—is almost always missing, and has evidently fallen out as a result of the casting of the congenital hair. Consequently the so-called Milia are not horny cysts but sebaceous cysts.

Possibly most of all the so-called *milia of scars, or the milia of healing eruptions*, which are found, for example, on lupus scars or after erysipelas or pemphigus, are also sebaceous cysts. In one such case, where in a healing tertiary syphilide a regular wreath of these small, miliary, white, somewhat transparent, elastic, vesicular "milia" appeared around every spot, they proved to be not true milium, *i.e.*, horny cysts, but sebaceous cysts, which had developed from the partial closure of the follicle entrance with horny layer, and increased sebaceous secretion. Of the larger, whitish or yellowish tumours, the size of peas, which develope in numbers especially on the scrotum, there is a short description by M'Murtry of Ochterlony's case, where the capsule of the sebaceous gland was very much thickened, and the interior of the cyst divided by hypertrophic connective tissue septa, and filled with a caseous, white, unpleasantly smelling mass.

The still larger cysts with open mouths, which develope singly or multiply on expressed acne pustules or other folliculitides, resemble, as a whole, the large horny cysts, with the difference, that remains of the sebaceous glands and usually also of the hair follicles are present, and the dilated duct of the follicle does not, as there, produce excessive masses of horn. In many cases, the periodical casting of the hair gradually leads to an accumulation of loose, long hairs in the follicle, as in dermoids in whose walls hair follicles are found, *e.g.*, in one case of Stelwagon.* Where the large sebaceous cysts develope from previously existing small horny cysts, *e.g.*, in Acne, the excessive horny production must, of course, previously be arrested; the rigid cavity, clothed with epithelium, to which the latter leads, is then continuously filled with fat from the remaining sebaceous glands. A similar substitution I have also observed in double comedones. In these cases is there first the opportunity for the formation of mixed horny and sebaceous cysts.

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* To this class also belong most of the early cases deseribed as hair fistulæ and hair-produeing cysts. The spontaneous rupture of true dermoids must be extremely rare.

(cc). *Syringal cysts.*

In the cysts of the coil glands, we have the same principles which rule the cystic formations of the follicles, but still more distinct, on account of the greater length of the duct. As yet we know only cysts of the duct and its prolongation through the epidermis, *i.e.*, of the sweat pore, not cysts of the coil; to put it shortly, syringal not spiral cysts. The contents of these cysts are more multiform than those of the follicular, which are usually only horny layer and sebum. There are syringal cysts, which contain a clear sweat secretion, similar to that met with on the surface. But in most cases, the contents show more formed elements, finely granular precipitates and drops, which are possibly always present in the sweat, and are only better recognised in the gradual evaporation in the cysts. This evaporation may go so far in older cysts, that in alcohol preparations, a faintly granular, solid cast of the cyst is seen, which appears to be the coagulated product of a hyalin albuminoid body. Fibrin and fat have not yet been recognised in the cysts. But sometimes numbers of leucocytes penetrate into the duct, and form abscess-like collections. The products of the epithelial walls of the duct do not usually mix with the contents—as in the follicular cysts; in most of them we have before us nothing but coil secretion, modified in different ways. This important difference is explained by the fact, that the duct of the coil gland is clothed by a cuticle, a homogeneous, firm, greasy membrane, while the infundibulum of the follicle shows only ordinary horny cells. Where the cuticle ceases, at the level of the granular layer, we sometimes have an epithelial growth, which closes the ducts by purely epithelial products, and consequently leads to a horny cyst. The congenital tumours of the duct (conf. congenital Syringoma), always show an epithelial growth, with hyalin degeneration, which leads to the formation of hyalin (colloid) cystic contents; this is owing to the slight development or complete absence of a cuticula in the embryonic period.

It is best to distinguish the cysts of the duct proper, *i.e.*, of the epithelial duct inside the cutis, as *Duct-cysts;* the cysts of the duct inside the epithelium, as *Poro-cysts.* In the latter, the hindrance to excretion always lies in the horny layer. In the former, the position varies in different cases; it may be at the level of the horny layer, in the prickle layer, or at the point where the duct enters the cutis. There is in this multiformity an important difference from the behaviour of the follicular cysts, which are all induced by a hyperkeratosis of the surface, and are mostly complicated by one of the duct. These facts also correspond to the well-known rule of many other dermatoses, that the thickest horny layers may still be penetrated

by open sweat pores, while a very slight hyperkeratosis is sufficient to close the mouth of the follicle. And these contrasts are very important from the standpoint of normal anatomy, for the horny cells only surround the sweat pore with their lateral angles, the follicle mouths with their surfaces.

Before we more closely describe the duct- and poro-cysts, it is perhaps not superfluous to say something of the nature of the coils. If these do not show proper cysts, round, enlarged cavities, in which the typical form of the coil is gone, they often enough show considerable simple dilatations. We have met with such, for example in Lichen and Ichthyosis, dermatoses in which the marked hyperkeratosis of the surface justifies the explanation, that here stagnation has taken place down to the end of the glands. This view is the more justified, as with the dilatation of the lumen, which may often be found without any causes of stagnation, a membranous thickening of the glandular cells towards the lumen takes place, which possibly alters the character of the cells as glandular cells, and causes them closely to resemble duct cells. In this affection of stagnated secretion, we have perhaps to recognise an analogy to the atrophy of the sebaceous gland cells under the influence of pure stagnation, and their re-conversion into simple prickle cells. We have seen very distinct dilatations in Erythema bullosum vegetans, even in varices, granulations and scars, without any plausible causes of stagnation, and without any aplasia of the gland cells. Most dilatations of the coils are consequently not due to stagnation of secretion, but are manifestations of inflammatory processes, progressive and regressive disturbances of nutrition of different nature. In other words: the reaction from the surface on the form of the coil is only slight, and not to be compared with the action of direct influences from the cutis. The study of the syringal cysts gives us a valuable confirmation of this. For in all these cases there is certainly complete stagnation of the secretion, and yet we never see marked appearances of stagnation. An otherwise normal character of the epithelia and muscles of the coils, appears to be sufficient to overcome the influence of stagnation of secretion.

1. *Duct cysts. Hydrocystoma.*

Just above where coil and duct join, the latter may show marked dilatation. This never extends the whole way to the surface epithelium, but affects only parts of the duct, which then appears spherical, ovate or pear-shaped, or, if there are two swellings, the shape of an hour-glass. The smallest of these cysts sometimes develope by a stagnation of wandering cells, *c.g.*, in Variola, Erythema bullosum

vegetans; the largest are simply stagnations of secretion. I have had the opportunity of studying all the forms, in old cases of Favus. Some are always found in lupus scars, in elephantiasic skin of different areas, and in ulcers of the leg. In one case I found, in a small spherical duct cyst in a case of Lupus, one single tubercle bacillus. The duct cysts show a regular, more or less thick coating of squamous epithelium, usually consisting only of two or three layers of cells, which vary very much in extension and flattening. No special cuticle is usually recognisable on the innermost layer. In all cases, the entrance of the duct into the cyst is easily seen, but it is usually very difficult to find any definite reason for the stagnation. This is easiest in the favus preparations, because the whole surface epithelium is compressed in places by the pressure of the scutulum, and is often laterally distorted. Distinct impermeable stretches of the duct, obliterations of the already narrow lumen, are not usually recognisable.

Hydro-cystoma is the multiple appearance of large duct cysts, accompanied by excessive hydrosis. This cystic formation, which is not uncommon in washerwomen, cooks, and females suffering from hyperidrosis, has been described by Jackson, Jamieson and Rosenthal as Dysidrosis faciei, and by Robinson, first as a form of Sudamina, but recently, in a very careful publication, as Hydro-cystoma. These are mustard-seed to pea-sized, semi-spherical, elevated, white, shining, transparent, thick-skinned, non-inflammatory vesicles, which develope sub-acutely, without any subjective sensations, and dry up and disappear without bursting. The contents are always clear, often somewhat sticky, and always acid.

Robinson has shown, in a whole series of these cysts, that, except for the coil ducts, all the elements of the skin are normal. At most, there is, in the upper layers of the cutis, in the older cysts, a slight leucocytosis. In the coils, which are here and there dilated, there stagnates a remarkably granular secretion. The widening of the duct begins somewhat above the coil, and forms, in the under part of the cutis, a cavity lined with flat epithelia, and filled with clear secretion. As it enlarges, it grows upwards, compresses the neighbouring structures, and flattens the papillary body and the epidermis. The covering of the cyst consequently consists of the epidermis, along with a thin plate of flattened papillary body, thus an upper layer of the cutis, while the cover of the Crystallina vesicle consists entirely of horny layer. From the vesicles of Miliaria and Pompholyx faciei, these cysts are distinguished by their seat under the prickle layer, and the absence of all inflammatory symptoms.

2. *Poro-cysts—Horny pearls—Prickly heat—Crystallina.*

The cysts of the sweat pore are, according to position, those of the

prickle layer or of the horny layer; according to their contents, *horny* cysts or *sweat* cysts.

A few words will suffice for the horny cysts, for we have already described them under Lichen. In certain forms of that disease (poral papules of Lichen obtusus, planus, corneus), they are specially characteristic, and usually recognisable clinically. If, as is often the case, they are the seat of severe itching, the patients themselves learn that the removal of the horny pearls removes the itching. They develope by the more active cornification of the cells around the sweat pores, along with closure of the lumen, and thus the cornified cells collect into spherical accumulations. The sharp distinction of these horny collections from their cornified surroundings is very remarkable. This begins with the concentric arrangement and welding of the horny cells to form a pearl.

The spots which appear in tropical Prickly heat have recently been described by Pollitzer as *sweat cysts* of the pore. In contrast to Miliaria rubra,* which is often confounded with it, and where we are dealing with inflammatory vesicles, the vesicles in Prickly heat develope, according to Pollitzer, who has had the opportunity of examining eight cases of this affection, as yet unknown in Central Europe, from the dilatation of the sweat pore inside the prickle layer. The vessels of the papillary body are dilated, as are the lymph spaces of the prickle layer around the cysts; according to Pollitzer, there is no inflammation, and very slight leucocytosis. The cysts at the commencement have exactly the form of a conical sweat pore; their broadest portion lies directly under the basal horny layer, their diminishing end at the level of the basal prickle layer. They follow, at the commencement, the windings of the pore, and appear, on vertical sections, as a series of dilated canals. As they continue to enlarge, they take an indistinct oval form, but are always localised underneath the horny layer, and thus sharply distinguished from Crystallina. Pollitzer finds the contents to consist, at the commencement, of clear fluid, containing a finely granular mass, with a few epithelia and leucocytes; the contents later become more cellular, and when they exfoliate are a mere indistinct cellular debris. Pollitzer lays great stress on a constant swelling of the horny cells, and a frequent preservation of their nuclei in rod-form, especially around the sweat cysts. The horny layer seemed to him like the swollen horny layer of a mucous membrane, and he is therefore inclined to attribute the hindrance to excretion, to a swelling of the horny cells from excessive imbibition of sweat, by which the pore is

* Pollitzer does not draw any distinction between Prickly heat and Miliaria rubra, using the latter as a synonym of Prickly heat; nevertheless, we owe to him the first thorough separation of the two affections on the basis of histologieal investigation.

obliterated in its passage through the horny layer. This explanation does not tally with the daily experience, that maximal swelling of the horny layer by water and alkalis (in washerwomen), which is much greater than that caused by the acid sweat, never causes a blocking of the sweat pores. Then the idea, that the swelling of the horny cells and the limited occurrence of rod-shaped nuclei in them * stamp the cornification as an incomplete "mucous membranous" cornification, is incorrect. Pollitzer describes and figures a well-preserved granular layer surrounding the cysts, and considers the localisation between the granular and basal horny layer as the most frequent. An artificial swelling of the horny layer from without, however great, never causes the granular layer to disappear, for the water cannot penetrate the basal horny layer; for that, an excessive saturation of the cutis is necessary. Consequently, so long as the granular layer is preserved, in prickly heat the surface cornification is certainly normal.

The facts given by Pollitzer are however amply sufficient to separate this affection, which had not previously been examined, and had been identified, simply from the statements of Hebra and Kaposi, with Miliaria rubra, from Miliaria. While in that there are signs of superficial catarrh of the skin, and the eruptions, like true vesicles, develope independently from the sweat pores, in Prickly heat there is no distinct inflammation, but only an accumulation of sweat secretion inside the pores. Perhaps in doubtful cases the presence of mast cells in the vesicle might be useful in the diagnosis of Miliaria, if they should not also be found in Prickly heat. In future investigations of the two affections, attention must be directed, histologically, to the behaviour of the sweat pores and the possible presence of bacteria, clinically, to the reaction and composition of the fluid. It is to be hoped that a thorough clinical differential diagnosis would follow this histological one, but it can only be in those (sub-tropical) regions where both affections are to be found. We will then see how the slight changes of the papillary body, and the slight leucocytosis, which Pollitzer observed, are to be regarded; these may very well be—like the very slight changes in the cutis in miliaria—symptoms of an inflammatory chemotaxis. The examination of the sweat pores in Prickly heat for bacteria is of great importance.

The recognition of the eruptions of *Crystallina* as *sweat cysts of the horny layer*, and their consequent separation as a simple agonal phenomenon, appear-

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* It is a matter of common knowledge, that under the influence of an abnormal pressure alone, the nuclei of the horny cells persist as rods.

ing without any signs of inflammation, in febrile diseases (typhoid, pneumonia) over large areas of the body, from the inflammatory Miliaria, was first accomplished by Török in my laboratory. By the adoption of the name *Sudamen*, and the attribution, usually without any anatomical investigation and merely according to the will of the author, of both affections to the sweat pores, and finally by the use of double names, such as Miliaria sudamen, Miliaria crystallina, confusion has been made worse confounded. When different histological conditions are recognisable, and can be brought into constant relation with different clinical symptoms, the provision of a clear and simple name is our duty. Thus we rather avoid the name Sudamen, because it suggests the function of the sweat, and at once and unnecessarily recalls old erroneous views. I have therefore, since Török's work, suppressed the confusing adjective, crystallina, and distinguish the inflammatory papulo-vesicular Miliaria, seen every day in summer, from the rare crystalline vesicles, usually only found *post mortem :* Crystallina.

Török found, in a well-marked case of pre-agonal Crystallina, that the wall of the vesicle was formed everywhere of horny layer, while the granular layer, prickle layer and papillary body showed no changes,

FIG. 34.—Crystallina.

Vesicles *in* the horny layer. Into the one to the left a sweat duct opens, and to it, above, corresponds a projection. In that to the right, the flattening beneath the vesicle is very evident.

in particular, no inflammatory changes. This horny cavity contained no inflammatory exudation, but before hardening was filled with a clear acid fluid. It lay directly above the basal horny layer, extended in different degree, and the rest of the horny layer, elevated and compressed, formed its cover. Török was often able to see a sweat pore opening at the under border of the cavity.

I have, since then, twice had the opportunity of examining the skin from a typhoid corpse, and in all the vesicles the same changes were present. The vesicles, which on the corpse were tensely filled, and in alcohol preparations empty, were seated above the basal horny layer, the rest of which formed the covering. With the rapid distention of the cyst, half of it projected into the skin, levelling all the underlying papillæ and ridges, or displacing them obliquely; the super-papillary prickle layer was reduced to quite a thin layer, which consisted of excessively flattened and elongated prickle cells. Neither in the papillary body nor in the prickle layer were there any other changes than those of mechanical deformity. I was able to find in central sections the implicated sweat pore,* which was in direct communication with the cavity, and whose upper end was distinctly conical. To a certain degree, this dilatation is physiological, for somewhat deeper in the basal horny layer the narrowest slit-like part of the canal is normally found. But the marked dilatation here is distinctly pathological, and shows that, at least at the commencement, we have a simple dilatation of the pore; a poro-cyst. It is questionable whether the whole cavity is to be regarded as an enormously dilated poro-cyst, or whether the pore soon gives way, and the fluid sweat makes a new cyst wall in the middle horny layer; whether, in the larger spots, we have a poral cyst or a sweat cyst of the horny layer. In favour of the bursting of the pore, and the existence of a sweat cyst of the horny layer, is the fact, that we often see in central sections a projection, hanging from the middle of the horny covering, which resembles the compressed remains of a pore, and further, the circumstance, that at the lower opening of the pore into the sweat cavity, the last spiral windings are seen dilated and flattened. Were the walls of the cyst to consist of the normally dilated pore, we would expect that the cells of the pore, so far as they run inside the prickle layer, would be drawn out of the prickle layer. What takes place probably is, that there is first a dilatation and cystic formation of the intra-corneal part of the sweat pore, which at a certain tension gives way, and the sweat is poured out into the central horny layer, and distends it into a sweat cyst. We can only clear this up by investigating the commencement of the affection, on vesicles taken from the living.

After the observations of Török and myself, the previous statements on Sudamen and the different forms of Miliaria in the text-books are easily sifted. The cause of the sweat retention in Crystallina is as obscure as in Prickly heat. It is indeed more probable,

* Hair follicles often open into crystallina vesicles, but always laterally; the sweat ducts are always found practically central.

that the narrowest part of the canal in the basal horny layer may be closed (prickly heat) than the externally pretty broad mouth of the canal (Crystallina), especially as obstructions by innocent foreign bodies (powder, dirt, varnish) never lead to the formation of Crystallina. Apparently, still unknown chemical influences, possibly specific sweat bacteria, play a rôle (conf. Cheiropompholyx).

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2. *Stagnatory Tumours of the Cutis.*

Angiectasis.

The angiectases, so far as they do not belong to the congenital stagnatory growths (Nævi angiomatosi), comprise a series of pretty harmless affections, which all develope from primary ectasis of the capillaries or veins, and are at most secondarily combined with hyperplastic changes. To these classes belong the superficial reddenings known as teleangiectases, then the papillary capillary varices of old people, and finally the varicose and cavernous changes of the larger cutaneous veins in general varix.

The teleangiectases appear symptomatically, and then usually multiple or in areas ; or as an independent disease of the skin, and then usually isolated. The former accompany especially those conditions associated with inflammatory hyperæmia, affecting the central area of the face (the butterfly area), which embraces the back of the nose and the middle of the cheeks, and in every general redness of the face is especially hyperæmic. It is especially seborrhœic Rosacea, Ulerythema centrifugum, and some cases of Lupus and Syphilis of the face, which give rise to the formation of Teleangiectases. Certain affections which lead to shrinking, as, for example, Xeroderma pigmentosum and circumscribed Sclerodermia, induce the development of Teleangiectases on other parts of the body also.

We find, in the former case along with a diffuse, slight, removable capillary redness, in the latter without it, a number of stretched, readily visible vessels, which frequently anastomose with one another, but form no regular net, rather showing a tendency to diverge radially from a central point. We must not be confused by the

name Teleangiectasis, and expect dilated capillaries of the skin. For the vessels described can only be dilated veins, and in those cases, especially where there is no diffuse capillary hyperæmia, we should rather speak of venous ectasis.

> Matters are somewhat different in the isolated teleangiectases, which especially occupy the centres of the cheeks, the point of the nose, and the eyelids. These appear in children and adults, first in the form of a very fine, blood red, somewhat elevated point, which corresponds to a circumscribed papillary varix, and can only be caused to disappear under considerable pressure of the diascope. From these, there soon extend, in different directions, almost straight cutaneous veins, and thus a star or a spider-shaped figure developes (so-called Nævus araneus). The angiectasis may remain at this stage or unite with neighbouring venous stars to form larger ectases.

Here there exists, in the central red point of the star, a smaller papillary varix, a true teleangiectasis, which is combined with the previously described venous ectasis. The regions of the face are predisposed to this combination, while the papillary varices, which are so frequently evident on the trunk of older people, usually show no venous processes around.

> The last named growths are pale red, soft projections, half the size of a pea, which appear to be composed of normal skin, and often completely disappear on pressure.

The smallest occupy the space of four to eight adjacent papillæ, which are variously distended by a varicose dilatation of the capillary loops, and are usually seen tensely filled with blood. In the less dilated vessels, one can sometimes find an arterial limb, moderately or not at all dilated, opening into the ampulla, which always communicates with the dilated veins of the sub-papillary circulation. The largest varices occupy the whole space of the papillæ, and usually show two distinct extensions, of unequal calibre, into the sub-papillary vascular net. The dilatation of the latter is limited to the part of the skin beneath the papillary varix, or extends a little, but never far, into the surroundings, and along the ascending vessels.

From observations on four such Angiectases of old people, we note that the stagnation begins in certain sub-papillary, venous branches, and distends backwards, first the venous, then the arterial branches in the papilla, the venous limbs of the papillary loops showing most dilatation. The advance to cavernous Angiectasis, which two of my preparations show, commences at the most distended parts of the papillæ, the vessels twisting around each other; and the folds of the vessel walls, which appeared like septa in the lumen, and separated the individual cavities of the varix from one another, are compressed and disappear.

Thus there develope larger cavities with very thin walls and widely separated endothelial nuclei, which the papillæ distend spherically; the epithelial ridge system between the latter is thinned, and gradually completely retracts from the papillary body; the prickle layer is flattened out and thinned. But the process does not stop here; the thin walls of the varix yield, rupture and communicate with one another, and cavities are formed. Indeed, in one case, I had to assume a multiple rupture of the varicose capillary into the surrounding lymph spaces, for the cavities were very close together, and many had the form of spaces, enclosing blood capillaries. In such a case, pressure could hardly empty the growth. Nor could it if a number of cavernous spaces were filled with thrombi, as often occurs in all varices, and especially in superficial ones. One of my cases showed a widespread coagulation; the thrombi, consisting of fibrin and a few leucocytes, were some of them marginal, while others completely filled the lumen of the cavity. In the former case, the rest of the space was filled by closely packed red blood corpuscles. But before the thrombus, there collected, in a number of dilated capillaries, a great quantity of leucocytes, which were distinguished by the fact, that without breaking down in the stagnated blood they almost all showed chromatin changes. The nuclei showed the most wonderful forms, especially stellate and antlered branching of the chromatin, also a breaking down into granules, but only rarely the normal clover leaf form. Many of these branched figures recall mitoses, but I have not met with true mitotic structures. This thrombosis and stasis in the cavernous growth has the special interest, that not one single red or white blood corpuscle has left the circulation, though the conditions for diapedesis are particularly favourable—one of the proofs of the fact that thrombosis and stasis alone are in no case sufficient for diapedetic bleeding of the skin (see bleeding).

The mechanism which leads to the development of Teleangiectasis is only sufficiently explained in exceptional cases. The dilatation from inflammatory causes probably depends on a chronic stagnation of blood, which, like leucotaxis, is directly brought about by the causes of inflammation; but there is, in addition, on the one hand, the facility with which those areas of the vessels of the face are always paralysed, and, further, in certain individuals, a special tendency to periodical flushing of the face; in other words, a specific facility, with which the central restraining ganglia of the skin of the face, in some persons, are paralysed. Therefore these ectases are first diffusely extended in the capillary region, before they advance to venous ectasis. The ectases on an atrophic basis are probably the result of a widespread obliteration of whole capillary regions. They are combined, from the commence-

ment, with some capillary varices or limited capillary hyperæmiæ, and, with these, represent the superfluous capillary and venous collaterals. The isolated teleangiectases, usually congenital moles, have no plausible explanation. Since they almost invariably appear in the centre of a small papillary varix, this is probably to be regarded as the primary appearance, and the radially-extending veins are only to be regarded as extensions of the ectasis to the neighbouring parts of the circulation. We are equally ignorant of the development of the capillary varices of older people; from the manner of their spread they must all have some superficial cause lying in the skin.

In this point, they all differ from the venous ectasis, which extends to the skin from varix of the larger veins. Here the cause (hypostatic hyperæmia) is known, and is under the skin. I have taken pieces of skin from eight different cases of marked varix on the back of the foot or the leg, which showed the distended veins shining red or blue, close under the surface, so that one expected a change in the cutaneous veins. The investigation gave such unexpected and such unanimous results, that I may briefly mention them.

In all the cases, the subcutaneous tissue and more or less of the lower cutis, are converted into a cavernous net-work, filled with uncoagulated blood. The spaces vary much in size and are very irregular, a few of them resembling smoothed-walled lymph vessels or veins, most of them, torn or very much dilated tissue spaces. Only few of them are regularly lined by endothelium; many are bounded by naked, a-cellular, collagenous bundles, which often project, as if torn, into the cavernous spaces, and only partially split them up. Usually one finds —more often laterally than in the centre—the cross, oblique or longitudinal section of a large, much dilated cutaneous vein, known by its smooth regular walls and endothelial lining; in some sections we can recognise a direct communication with the surrounding cavernous spaces.

The most peculiar feature in this cavernous tissue surrounding the cutaneous veins, is, that it is pretty regularly rounded outwards. While the central meshes are angular and quite irregular, the external spaces show a certain rounding on their outer side, as if they were enclosed by a common sheath. But with a nuclear or protoplasmic stain there is no sign of this. An elastin stain is necessary. Then we recognise at once the chief vein of the cavernous cord, by its distinct elastic lamella, and the place where it has given way, by the disappearance of the elastin. This extends beyond the opening, so that we must assume that it is due not to a sudden circumscribed trauma, but to a prolonged and widespread effect on the elastin. The collagen also, in the centre of the vascular cord, which forms the septa of the

cavernous tissue, is largely free from elastin, completely so, so far as it belongs to the subcutaneous tissue. Only at some distance from the cavernous cord, do we see the normal elastic tissue, but here it begins, not, as usual around new growths, with a few fine fibres, but at once with a coarse wreath of fibres, with an elastic ring. This it is which induces the otherwise invisible margining of the cavernous cord from the tissue around, whose influence we see at a glance, in its regular, enclosed, circular arrangement around the complex of cavernous spaces, even where normally no elastin or very little is present, as in the fatty tissue. For the formation of this new elastic ring, the elastic lamella, not only are the elastic fibres present closely arranged, but there develope new ones, where none were previously present. This elastic new formation runs through the tissue, without regard to the course of the other fibres, and apparently only dependent on the pressure of the blood, which has burst through into the cutaneous tissue, and causes the elastin to arrange itself tangentially into a protecting wall. Thus it is not remarkable, that, in different preparations, the ring is often enough not complete, and is very differently developed in different places. Sometimes it is completely absent, and is replaced by thick collagenous cords, sometimes two incompletely formed elastic lamellæ overlap; where the central vein lies peripherally, the elastic new formation passes into the elastin of the vessel wall.

The whole change then consists in a yielding of a part of the venous wall, but this takes place so gradually, that there is no bleeding, for, first from the adventitia, then from the cutaneous tissue around, layers are deposited around the vessel, and thus the circulation is preserved. Thus a section of the skin surrounding the vein is converted into a cavernous tissue, a thick vascular cord of spongy structure, which is separated from the surroundings by a new elastic lamella. This latter is the only new formation; the cavernous tissue owes its origin simply to the penetration of the blood into the peri-vascular, previously healthy tissue; it is an Angiectasis, not an Angioma.

It is clear that this process of transformation of the skin into cavernous tissue leads to a condition, which, on the one hand, aids the development of Ulcus cruris, and on the other, very much favours continuation of venous bleeding from any cause. For such a sponge cannot possibly show sufficient elastic reaction. The influence of this distinct blood stagnation on the cutis around is always shown in the same way. The fat of the subcutaneous tissue largely disappears, even where it is not directly compressed by the cavernous venous plexus. In its place appears a coarsely fibrillated connective tissue, with new-formed elastic fibres. The latter form no fine net as in the cutis, but dense bundles of thicker fibres, which lie, as if pushed

together, between the broad, new formed collagenous rafters. In this condensed subcutaneous tissue, streaks of fat, the remains of previous considerable fat lobules, were found embedded.

The collagen and the elastin of the cutis are little altered, except in the papillary body and the connective tissue around the coil glands. In these two places the collagenous tissue is converted into a homogeneous, only indistinctly fibrillated, swollen tissue, in which the elastin disappears. Thus the papillæ are thickened, of long cylindrical form, and compress the ridge system of the epidermis into small cords. Even the horizonal plate of the papillary body is thickened, homogeneous, and free from elastin. While in normal skin the sub-epithelial elastic net surrounds, in the well-known garland form, the depressions of the epidermis, here a superficial net of elastin lies only at the base of the papillary body, widely separated from the epithelium, and only a few fine fibres penetrate into the homogeneous, thickened tissue of the papillæ.

The perispiral connective tissue is similarly affected; it is thickened, homogeneous, indistinctly fibrillated, and united into a uniform mass, in which the loops of the gland are embedded. But the glands themselves are still more altered; they are evident in all preparations by their increase in size. The lumen is always dilated, the individual epithelia are large and multiplied, the protoplasm of the older ones is clear and homogeneous, that of the numerous younger ones granular and deeply stained. In many places the external contour of the lobules of the gland is irregular, and we note here that the musculo-elastic membrane of the gland is absent; it has evidently been taken up by the altered perispiral tissue. But in most glands, growth is added to these appearances of dilatation, and there are buds of epithelium, which in some cases go on to Spiradenoma: a true Adenoma of the coil glands. These adenomatous growths are, in my preparations, limited to the margin of the altered perispiral tissue, and show no tendency to invade the rest of the cutis.

The duct of the coil gland is widened in the same way, the epithelium is thickened, the homogeneous membrane becomes broader and stains more deeply, the lumen is dilated, and the duct shows its general enlargement by its cork-screw windings.

Some glands directly margin the cavernous tissue, and are then, as a whole, pushed to one side, often flattened, and separated from the cavernous tissue by an elastic lamella. Then there is usually developed, on the opposite side of the gland, a new elastic membrane, so that the loss of all the fine fibres directly surrounding the gland, is replaced by a coarse elastic shell, which encapsules both the gland and the perispiral homogenised tissue.

In contrast to the coil glands, the lanugo hairs suffer no great changes, and those of the epidermis are, apart from the thinning of the ridge system, inconstant, and dependent on complications.

There are never appearances of inflammation in the connective tissue around, never an increase in size or number of the connective tissue cells; nor is there an emigration of leucocytes, in spite of the slowing of the blood stream. But we often meet with distinct deposits of pigment, remains of previous hæmorrhages, and sometimes these are surrounded by a moderate new formation of elastic tissue, of the most varied form, which has probably served to encapsule and heal previous cavernous spaces.

Inside the cavernous angiectases, we find accumulations of pigment in the larger septa, collections of leucocytes in certain of the cavities, and an ever-increasing disintegration of the intra-cavernous connective tissue.

Lymphangioma and Lymphangiectasis.

The lymphangiomata of the skin are usually treated in the text-books as a supplement to the angiomata, and commonly regarded as a perfect contrast to them. But if one will compare the different forms of tumours of the blood vessels with the lymphangiomata, he will see that the lymphatics only correspond to a limited part of the circulation, namely, only to the venous, and that consequently the mechanism of Lymphangioma can, at most, be put in parallel with the specific venous Angioma, with Varix. But if the analogy with the Angiomata is by many taken too far, and the Lymphangiomata are too much regarded as tumours, it must not be forgotten that other pathologists make the distinction very narrow, and maintain, for example, the occurrence of large lymph vessels in spaces where normally none are found, and ascribe all other appearances to Lymphangiectasis (Birch-Hirschfeld). The indeterminate distinction between Lymphangioma and Lymphangiectasis, which different authors draw so differently, is related to the want of clearness of the definition of the tumours of the lymph vessels, which evidently depends on the peculiar character of the lymphatics.

While the circulation is a complete system of closed canals, the lymphatic circulation commences with spaces, which have no wall of their own. The hypertrophy of the walls, which is the necessary criterion of hypertrophy of any canal system, is not available in an important part of the lymph track, and one is inclined to regard the hypertrophy of the commencement of the lymph vessels, somewhat paradoxically, as an ectasis of the lymph spaces, *i.e.*, in the enlargement of something non-existent. It would be more correct, if, recognising

the incompleteness of the walls of the lymphatics, we determined only to recognise hypertrophy of the system, when the elements of the walls were multiplied, or where such appeared where previously absent. The varix of the lymph vessels would then come as well under the definition of Lymphangioma, as the endothelial formation in those places where normally lymph spaces without endothelium are found.

Taken thus purely anatomically, the question whether we are dealing with new formation of lymph vessels, or only with their dilatations, is, on careful examination, always answerable. But it is otherwise, if we regard, at the same time, the etiological side of the question, *i.e.*, if we seek the reasons which may have given origin in certain cases to a dilatation of the lymphatics, or in others, to a growth of the elements of their walls. The reasons for a dilatation in a canal system adapted to the removal of the tissue juice, must lie, either in an increased pressure of the fluid contents, or in some primary defect in the wall. We may ignore the latter at present, although in many dermatoses, accompanied by scarring atrophy (Ulerythema), it plays a part. For these processes have a completely regressive character, and have never been related to the formation of Lymphangioma. They have for us a negative value, for they clearly prove that a *multiplication of the lymph spaces* of the cutis alone never induces the symptoms of lymphangiectasis, in the ordinary sense of the word. Thus, the only etiological factor to discuss is the stagnation of lymph.

There has been much argument whether lymph stagnation, as such, can of itself be the cause of the formation of Lymphangioma and Lymphangiectasis, and while, previously, under the influence of Wegner's work, the influence of lymph stagnation was supposed to be sufficient—and even possibly over-valued, since the work of Langhans, the opposite has held, and the process has been attributed solely to a growth of the walls of the lymph vessels. Especially Nasse, Klebs and Török have recently maintained the latter view. Now, it is quite clear, that a simple dilatation of the lymph vessels, without any cellular proliferation of the walls, could never explain the appearances which are recognised as Lymphangioma. Were there a simple stagnation of lymph, without any other process, which, overcoming the valvular apparatus, retained the lymph in the tissues, the result must be, first, a dilatation of the radicles of the lymph vessels, then a giving way of their endothelium, whereby the lymph vessels would be converted into lymph spaces, and the Lymphangiectasis into an interstitial œdema. It is this wearing away which finally converts the varicose Lymphangioma into a cavernous one, and for certain terminations of the whole process, we must admit the predominance of simple stagnation of lymph. But this would never explain even the smallest lymph

cyst of the skin; a superficial increase of the lymph vessels, along with a dilatation, is necessary to explain the appearance, and this assumes cellular division in the walls. No one has thought of a simple lymph stagnation alone, and even Wegner, who lays most weight on stagnation, admits that ectasis and hyperplasia always go together. The point in question now is, whether a simple stagnation of lymph is the primary cause, which alone suffices to set up the proliferation of the walls and to maintain it, so that the latter appears secondarily, and always only in relation to stagnation; or whether, on the other hand, proliferation must be regarded as the first change, which extends of itself, and to which, stagnation—ultimately a favouring factor—may in different degrees be added. The latter view here interests us most, for Török has recently maintained it for Lymphangioma capillare varicosum of the skin.

If one reads those authors (Langhans, Esmarch and Kulenkampff, Nasse, Schmidt) who, after Wegner, discussed the pros and cons of this question, we see in all of them the attempt to maintain the physiological facts, which teach that simple ligature of the thoracic duct is never followed by œdema, and that in prolonged organic closure of the thoracic duct, both œdema and lymphangiectasis may be absent. But when they declare, on one hand, that even a definite central lymph stagnation is not in any way sufficient to explain an Angioma or an Elephantiasis lymphangiectatica, they should, on the other hand, greet with satisfaction the fact, that no one has been able to determine such in circumscribed Lymphangiomata, for then all experience would be agreed. Instead of this, there is the somewhat inconsistent tendency to bring some of these changes into connection with central obliteration of the lymphatics. Thus Esmarch and Kulenkampff quote cases of Wegner and Langenbeck, and Virchow's old observation on the calf (p. 171), as instances of the positive action of such hindrances, without noticing that our present knowledge has given a fresh explanation to these facts. Nasse admits, at least for the diffuse ectases of the lymph vessels, a central obliteration as a sufficient cause. Even Langhans, although fully convinced of the insufficiency of central stagnation, "in order to be quite sure" that the lymph vessels were free, used injections, and rejects Wegner's theory of macro-glossia, mainly on account of the fact, that the seat of the resistance is difficult to demonstrate. Were a proper obliteration of the lymph vessels once found in a Lymphangioma, the most competent authors would not refuse to recognise here, exceptionally, sufficient cause for the closure, although we must at present say that such can *never* be the true cause, and that we should never seek for such in the lymph trunks.

Here, as already in the chapter on Œdema, and a second time in that on Elephantiasis, we see distinctly, that the present general views on these facts—as they are stated in the very careful work of Nasse—can only be applied by one seeking the cause of the stagnation, not at the proper place, *i.e.* round the veins, to which physiology and experimental pathology have long pointed. I am convinced that in all those cases* in which authors were able to find the thoracic duct compressed, a primary and much more important compression of the neighbouring veins was overlooked. In many cases, in which even thrombosis was admitted in the large veins, the authors have not thought it worth while to discuss any relation to the lymphangiectasis (*e.g.* Nasse, case 18). There is never any thorough investigation of the calibre of the large venous trunks, even if there are definite statements about the arteries and lymphatics (case of Langhans'). And yet, *only in the large veins*, if anywhere, is a *central primary stagnating cause* to be sought. Once attention is directed to this, one will be able—though not with summary statements about permeability or normal behaviour of the blood vessels—to decide this first question of a primary central stagnating cause. To my mind, such are present in very widespread Lymphangiomata, especially in Elephantiasis lymphangiectodes congenita.

Unable to find causes of stagnation in the larger lymph trunks, Esmarch and Kulenkampff as well as Nasse, turned to local causes of stagnation, and rather remarkably to somewhat incorrect appearances or mechanical alterations and aberrations of the lymph vessels of the affected region. As if every resistance, if it did not cause a stagnation in the veins of the affected region, were not completely irrelevant to the outflow of lymph from it! Nasse remarks very truly: "The complete closure of the affluent lymph vessels is, in the circumscribed Lymphangiomata, not only not proven, but in most cases certainly not present," and he adds: "Although it cannot be denied, that slight stagnation of lymph may be, and often is present, *for without it one cannot explain the distension of the lymphatics.*" In this connection I regard it as fortunate, that, up to now, such local occlusions have not been found, and that the scarring, shrinking local change of the surroundings, assumed by Rindfleisch, is not applicable to Lymphangioma. For then attention would be diverted from the proper source of every lymph stasis, the venous system.

Török rejects, altogether, local stagnation as sufficient reason for the capillary varicose Lymphangiomata of the skin, and is in favour of the theory of neoplastic development. He notes, that such a cause of stagnation could only act at the same time on the endothelia of all the

* With the exception of lymph stasis of the intestine.

papillary lymph vessels of an area, while, as a fact, we find, close together, sometimes large lymph cysts, sometimes simple cellular infiltration. This, I would remark, by no means contradicts the assumption of a primary stagnation, for the rapidity and the amount of development of Lymphangiectasis inside an area may show the greatest differences. Just as in an elephantiasic leg we only see, here and there, vesicular protuberances over the skin, although the cause of stagnation is everywhere the same, so there must exist differences in the power of resistance of the different segments of the papillary body, which determine the topographical arrangement of the varicosities. Török further rightly notes, that in another skin disease, Urticaria pigmentosa, an habitual œdema is present in the papillary body, without the lymphangioblasts being stirred up to proliferate. But this very example teaches, that, by prolonged lymph stagnation, other progressive changes are induced, *e.g.* the accumulation of mast cells and pigment. Further, the new formation of any kind of tissue, under the influence of blood and lymph stasis, on the elephantiasic leg, is a daily appearance, and the formation of Lymphangioma and Lymphangiectasis is too closely bound up with it to throw aside the thought of a stimulation of the lymphangioblasts to proliferation by stagnation, even if this were only exceptionally recognised. I regard the local causes of stagnation, when such are found in the proper place, in the venous system, as quite as able to induce the lymphangiomatous process as the angiomatous, especially when they act on embryonic tissue.

But what is the opposite side of the whole question? Can we simply satisfy ourselves with the proof, that, in the neighbourhood of pre-existing lymph vessels, spindle cells are seen, showing fine canals between them, and in connection with the lymph vessels? Do such observations, which may evidently be regarded as an attempt at the formation of blood vessels, give us any guidance as to the formation of the complete lymphangioma? We know very well that the buds of a pervious capillary may be opened out, and become part of the vascular net. But where is the power and the pressure, corresponding to the blood pressure, in the lymphatic buds? And these must not only attain the ordinary calibre, but become varicose. More, this distension of the new territory advances in the opposite direction to the lymph stream. It does not appear at the pointed ends of the new buds, where the lymph enters, but at the broad end, through which they empty their contents into the varix.

It seems, then, that the commencement of the Lymphangioma in the endothelial spaces, recognised by Nasse and Török, has not done much for us. As in all the older authors, in particular Wegner, we are always pointed to a power and a pressure, which acts in the opposite

direction to the natural lymph stream, as soon as we wish to explain the ectasis of the lymph vessels in Lymphangioma. An expansive power of the endothelia, sufficient to cause the disappearance of the inter-tissue, will hardly be looked for; there is difficulty enough in recognising these delicate lymphangioblasts.

What is this power which acts against the lymph stream? The simple accumulation of lymph in the tissue, by venous stagnation, by the same stagnation of which we have just assumed that it can stir up to proliferation all the elements of the tissue, is not enough. For then a new formation of lymph vessels, to a greater or less degree, would accompany every stagnatory dermatosis. But we see only interstitial œdema, *i.e.*, dilatation of the lymph spaces and simple dilatation of the main lymph vessels, while the connection of the tissue elements is loosened. This circumstance completely corresponds to a centripetal saturation of the tissue with fluid, the lymph escaping freely through the lymph vessels, which, instead of the veins, are now busy with absorption. But the conditions in Lymphangioma are otherwise. The surrounding tissue is of normal firmness. Only the pre-formed, excavated canals dilate to a maximum, so that some of them compress the tissue around, others, following the lymph spaces, communicate with them, and bud. Such a change assumes necessarily a force acting centrifugally backwards on the pre-formed lymphatics, while at the same time the saturation with tissue fluid must only be slight, at least in the varicose Lymphangioma. For otherwise, in the general œdema, the sharp limitation of the lymph vessels would be lost, and a compression of the neighbouring tissue by them not possible. This centrifugal force can only be sought and found in a stagnation in the route of the lymphatics.

We consequently come to the conclusion, that the so often sought resistance in the lymph vessels, which alone can never produce a Lymphangioma, is absolutely necessary for the explanation of that extension of the lymph vessels, Lymphangiectasis, which accompanies the Lymphangioma. Alone, it cannot produce Lymphangioma, because the lymph is not arrested by it; it gets out freely through the veins. On the other hand, every venous stagnation must lead to Lymphangiectasis, and may lead to Lymphangioma, since it opposes a resistance to the lymph vessels. *Every Lymphangiectasis consequently requires a double resistance to the venous and to the lymphatic circulation; and every Lymphangioma, thirdly, an abnormal power of proliferation of the endo- and perithelia.* It seems to me beyond question, that in future all these conditions must be sought in every individual case, and as our methods become more perfect, they will, no doubt, be found.

In many cases, the resistance to the venous and lymphatic circulation is the same, as, for example, where the pressure of swollen glands or of scars comes into play, and there are indications in literature that these cases are not uncommon; but attention has as yet been almost exclusively directed to the lymphatic circulation, and therefore they were unnoticed. But it is not necessary that the seats of resistance should be the same. We often see a peripheral lymphatic stagnation added to a central venous one; more rarely the opposite, for central obliteration of the thoracic duct and the larger lymphatics is rare. The nature and the seat of the lymphatic hindrance must vary very much, according to the nature of the Lymphangioma. A varicose dilatation and elongation of the lymphatics of the leg, as in the case of Langhans, with free passage of the lymph, represents a resistance of the same character as in varicose veins of the leg, a sort of hypostasis of the lymph. The formation of varix of the papillary lymph vessels alone presupposes some limited resistance at the under cutis margin, such as a congenital circumscribed absence of cutaneous lymphatics, or a scar-like obliteration of them. The vesicular protuberances of the lymph scrotum indicate a blocking of the lymphatics of the scrotal skin by parasitic thrombi. In the two latter cases, the equally necessary resistance to the return of the lymph by the veins, may be founded on the same conditions.

The *cavernous* Lymphangiomata of the skin require the same conditions as the varicose, both resistance to the venous outflow, and endothelial growth. They may develope in two different ways, according to the pre-existing distribution of the lymphatics. Where a net-work with relatively small lymph spaces exists, as in the cutis and in the papillary body, the cavernous formation is indirectly produced by wearing away of the walls, as the varices increase in size. The cavernous transformation is therefore always limited, and never pure. But if the lymphangiomatous process attack the hypoderm, where, in addition to very large lymph spaces, very few permeating, and hardly any true lymph vessels exist, the lymph spaces expand into cavernous, communicating cavities, and, at least most of them, being clothed with endothelium, assume the character of lymph vessels. But it is clear, that a severer venous stagnation, accompanied by œdema, may, by dilatation of the lymph spaces, produce similar conditions, even in the cutis, and that, even without the mediation of a varicose Lymphangioma, and without any erosion, a cavernous one may develope. Such parts are found in severer congenital Elephantiasis, in the skin (case of Bryk). The favourite seat of the primary cavernous lymphangioma is the hypoderm. There may be added to this a cavernous lymphangioma of the subcutis, and a varicose one of the cutis and the papillary

body, which shows the importance of the pre-existing texture of the tissue, in connection with the form of the Lymphangioma (*e.g.*, cases XIII. and XIV. of Nasse). In other cases, the formation of papillary lymph varix is combined with a hypodermal cavernous Lymphangioma on the surface of the skin, while the lymph vessels inside the skin are only moderately dilated (cases of Elephantiasis congenita, case XVII. of Nasse). Such cases are also explained by the increased elastic resistance of the cutis proper.

Were there any doubt that Lymphangioma always represents a direct stagnatory resistance to the lymphatics, it would be removed on considering the third form of Lymphangioma, the cystoid form. For in many cases it is seen, that the cystoid Lymphangioma, which developes, especially on the neck, in the axilla and under the angle of the jaw, directly proceeds from a cavernous one, so that different parts of the growth show the type of the two forms. Yet the explanation of the cystoid formation, which all authors adopt, is only possible on the assumption of a proximal resistance in the lymphatics, or even their absolute closure. These forms are frequently congenital, and it suffices, for the sake of example, to ascribe the cystoid transformation of a cavernous lymphangioma of the hypoderm simply to the absence of the few direct outlets from the lymph spaces of the hypoderm, venous stagnation being present. The transformation of a varicose Lymphangioma of the papillary body into a cystoid one, is not so simple, but it appears, in view of the observations of the French authors (Besnier, Sacquet, Darier), to occur. The outlets here are too numerous to undergo the same complete closure as in cystoid transformation. The absence of rapid filling of the spaces, after puncture, does not definitely prove, as Török noted, their complete cystic closure, for we do not yet know the absolute quantity of lymph produced in these very slowly growing or stationary tumours. But we must admit, that the larger the spaces are, and the more marked the hindrance to outflow is, the more pressure must be produced on the skin around, and thus is induced a condition of complete encapsulation of the cavity, which comes very near cystic closure. Certainly it contributes to this form of cystic transformation of the papillæ in the Lymphangioma, whose occurrence I do not doubt, that the extension of the Lymphangiectatic process from the papillary body to the more resistant cutis propria always meets with difficulties.

The partly hæmorrhagic contents of many Lymphangiomata of the skin have recently given rise to a controversy, as yet undecided. Wegner has ascribed it to hæmorrhages in the lymph spaces; Nasse believes in a combination of Lymphangioma with Hæmangioma. Now it is clear, that the invariably concurring stagnation of blood may very

well lead to dilatation of the vessels, such as appears between the Lymphangiomata of the papillary body. Venous stagnation alone would explain no Angioma, but the transformation of a simple existing Angioma into a varicose or cavernous one might be due to it; for the small Angiomata, which are now and again found among Lymphangiomata of the papillary body, show the same varicose and cavernous form as they do. Indeed, there is almost a replacement of the varicose lymphatics by varicose blood capillaries of the papillary body, and there are, in other Lymphangiomata, now and again, angiomatous insertions. Nasse mentions a typical example of this coincidence, in a female infant, where deep red, vesicular protuberances, on the surface, corresponded to the deep-lying Angioma, and clear ones to the deep-lying Lymphangioma (case 18). There is nothing remarkable in analogous new formations being combined, and there may certainly be, especially in congenital Elephantiasis, a true mixture of both conditions. (Esmarch and Kulenkampff.) But there remains the question, whether the blood-containing cavities, inside the lymphangiectatic parts, are true Angiomata; a question all the more justified since these Lymphangiomata have been (I agree with Török), incorrectly considered as degenerated Hæmangiomata. In this relation, it is to be remembered, that the existence of Lymphangiomata, especially of these Lymphangiomata of the papillary body, is not favourable to the development of true Angioma, especially of Cavernous Angioma. The greater the lymphatic pressure inside the Lymphangioma, the more are the blood vessels pressed to a side, and the adjacent capillaries narrowed, in spite of the general increase in blood pressure. The lymph pressure overcomes the venous pressure, and if an activity of the capillary endothelia could really cause a new formation of blood capillaries inside the Lymphangioma, these would hardly reach such a distinct varicose dilatation as the lymph vessels. It is more likely, that, under these conditions, with absence of endothelial growth of the blood capillaries, venous stagnation should lead to rupture of some of them, for they are surrounded by ectatic lymph spaces, and bereft of their protective connective tissue. Even the removal of the lateral pressure, on emptying the lymph vesicle by puncture, leads to bursting of the exposed blood capillaries. These bleedings in the lymph spaces, which are clinically recognisable, have often been confused with Angiomata of the papillary body. We find, in such cases, the contents either simply blood, a mixture of blood and lymph, or a blood coagulum. In other cases, the blood-containing cavities pass directly into the blood capillaries, and here the question arises, whether an angioma is present, or whether the burst blood capillaries have simply occupied the ectatic lymph spaces. I incline to the latter view, first, because I cannot convince myself of the existence of an angiomatous process in these

cases, and then for the general reason, that the conditions immediately around the varicose Lymphangioma are not favourable to the development of such varicose Angiomata. In my view, this apparent complication with Angioma is always due to rupture of blood capillaries.

We come next to the difficulty of distinguishing Lymphangioma from Lymphangiectasis. That these two conditions are very nearly allied, is readily understood. Both have, in common, the veno-lymphatic stagnation, and a universal endothelial growth. But in Lymphangioma this is not all; the excess of cell material is evident either in a thickening of the wall, or in an elongation of the vessel. We are not always in the position readily to recognise an excess, and here lies the difficulty of distinguishing the two. However great the dilatation of the lymph spaces, that is not sufficient for the diagnosis of Lymphangioma, any more than the number of the lymph spaces. By forcible injection of all the lymphatics of the skin, we would have Lymphangiectasis and not Lymphangioma, even if all the lymph spaces were clothed with endothelia. Only when the border of the true lymph vessels reaches to the lymph spaces, so that the former extend into the domain of the latter, do we have an elongation of the wall, and thus a Lymphangioma. Thus are formed the varicose lymphangiomata of the papillary body. The endothelial tube twists and winds all through the papilla, while usually it is only in the under third. And in the Lymphangiomata of the larger vessels, we have the same winding and elongation, as well as dilatation, but we have, as a further sign of progressive change, a thickening of the wall. More difficult is the determination of true growth in the cavernous Lymphangiomata of the subcutaneous tissue, for here we have only an enlarged edition of the normal structure of the lymph spaces. But, on account of the considerable size which these tumours reach, there has been no difficulty in the diagnosis between Lymphangioma and Lymphangiectasis, any more than in the cystic forms. In Langhans' case, convolutions of lymph vessels extended from the larger trunks into the fatty tissue, which usually contains no lymphatics, so that here the lymphangiomatous nature was beyond doubt.

If then, in most cases, a line may be pretty well drawn, it is to be noted that little scientific progress is made, for both processes are in the main identical, and even in Lymphangiectasis, there must be some endothelial growth, for a continuous endothelial covering developes. We may put it thus: Lymphangioma has really no true analogy with Hæmangioma, with its primary tendency to growth, but is a process which depends on primary dilatation and secondary reactive growth, and is therefore, all along, comparable to varicosity of the blood vessels, as I have already indicated as possible, in view of the analogous function of veins and lymphatics.

After this general pathological discussion, we may briefly refer to the histological results, which closely resemble each other. Without making any artificial division between Lymphangioma and Lymphangiectasis, we divide all the cases into three sections, according as the *papillary body*, the *hypoderm*, or the *subcutaneous lymphatics* are mainly affected. This anatomical division accords with the clinical conditions, since it pretty well corresponds to the three different characteristic forms, viz., the *lymph vesicles*, the lipomatous-like *lymph tumours*, and the special, so-called *Lymphangiectases*. This division is more appropriate to the acquired, or rather the forms appearing later on a congenital basis, than to the truly congenital, and especially to the so-called Elephantiasis lymphangiectodes (*q.v.*), for the firm cutis of adults is not favourable to the formation of purely cutaneous Lymphangiomata, and, with few exceptions, we meet here, only papillary and hypodermic tumours.

The Lymphangiomata of the papillary body appear in two well-characterised forms: the isolated, pure *Lymphangioma superficiale* (Lymphangioma circumscripta), and that superficial form which has a vesicular appearance, and is associated with the deep-lying Lymphangioma. The latter has become familiar through Morris' publication in the International Atlas. The name there used: Lymphangioma circumscriptum, indicates a contrast to Lymphangioma tuberosum multiplex: but it seems to me more important, in view of my division of all forms of Lymphangioma, to indicate the *purely superficial* character of this disease. While this has a nævus-like type—although developing long after birth—and is now and again combined with other congenital skin affections (cases of C. Fox, Friedberg, Busey and Köbner), there are, among the vesicular protuberances of the second form, several which develope on the basis of an infectious disease of the skin, and their highest development is found in the so-called lymph scrotum of tropical elephantiasis filariosia. The first form rather represents the Lymphangioma of the papillary body, and is sometimes accompanied by warty-like epithelial growth; the latter more often shows the type of pure lymphangiectasis of the papillary body, and tends in general to rupture and lymphorrhœa.

All Lymphangiomata of the papillary body tend to show the varicose form, which sometimes secondarily becomes cavernous. Those of the hypoderm are all along cavernous, and, after lasting some time, are partly or completely converted into mono-locular cysts or collections of them.

The subcutaneous Lymphangiomata also fall into two natural groups, of which one is a peculiar, rare skin disease. It is *Lymphangioma tuberosum multiplex*, which Pospelow has so clearly described.

Possibly the case of van Harlingen is the same. The other group is formed by the solitary, moderately lymphangiomatous tumours of the neck and the upper region of the chest, which are often enough clinically and anatomically noted by the surgeon. Many of them are congenital, and others depend on a congenital basis, but there are also cavernous Lymphangiomata, which are evidently of later development. These we will consider again under malformations.

The whole of the third class of Lymphangiomata, those of the subcutaneous vessels, is mainly congenital. But again there are some which are traumatic, or due to some unknown cause; therefore we treat them here. The three cases of lymphangiectasis of the elbow, which Nélaton observed in bleeding scars, illustrate how we can experimentally produce Lymphangioma by simultaneous wounding of the lymphatics and veins of the same region.

A.—*Lymphangioma of the Papillary Body.*

(a). *Lymphangioma superficiale simplex* (Lymphangioma circumscriptum).

Warty-looking spots, which appear in children or young people, on the face, neck, or shoulders, and consist of groups of small, transparent, vesicular papules. At the apex of the papules, as well as between them, there are found bundles of capillary vessels, which give the growth a marbled, piebald appearance. On puncture, a clear albuminous fluid escapes, and the spaces sometimes fill with blood. Some of them already contain blood, and look like small Angiomata.

According to Török's investigations, carried out in my laboratory, the histological changes are almost confined to the papillary body and the sub-papillary layer. The epithelium is only passively thinned, the prickle layer down to two rows; the epithelial ridges are, as a rule, thinned and shortened, but are sometimes a little enlarged. Now and again the horny layer is condensed. The papillary body is occupied and distended by wide cavities and winding canals, of irregular round or oval form, which open with conical mouths into one, rarely two lymph capillaries. The subpapillary spaces are smaller, and at their ends they pass distinctly into lymph capillaries. These are all varicose, from the sub-papillary stratum up to the epithelium; as they further enlarge, and the thin walls are worn away, large irregular cavities develope. The papillæ, which are free from varicose lymphatics, as well as the cutis lying underneath, show collections of cells, more towards the centre of the growth than at the border, and least around the largest cavities. The cavities are completely covered by endothelia, whose bodies are more swollen in the smaller dilatations than in the larger. In some of them there are giant cells, with as many as

twelve vesicular nuclei ; the cells are sometimes marginal, but apparently belong to the contents of the cysts, which are made up of coagulated, leucocyte-containing lymph, or blood, or both. The blood-containing varices are in connection with blood-containing capillaries. The blood vessels also, especially the superficial veins and capillaries, are dilated and surrounded by accumulations of cells; they evidently share in the process. The mixed contents of many cavities are to be attributed to

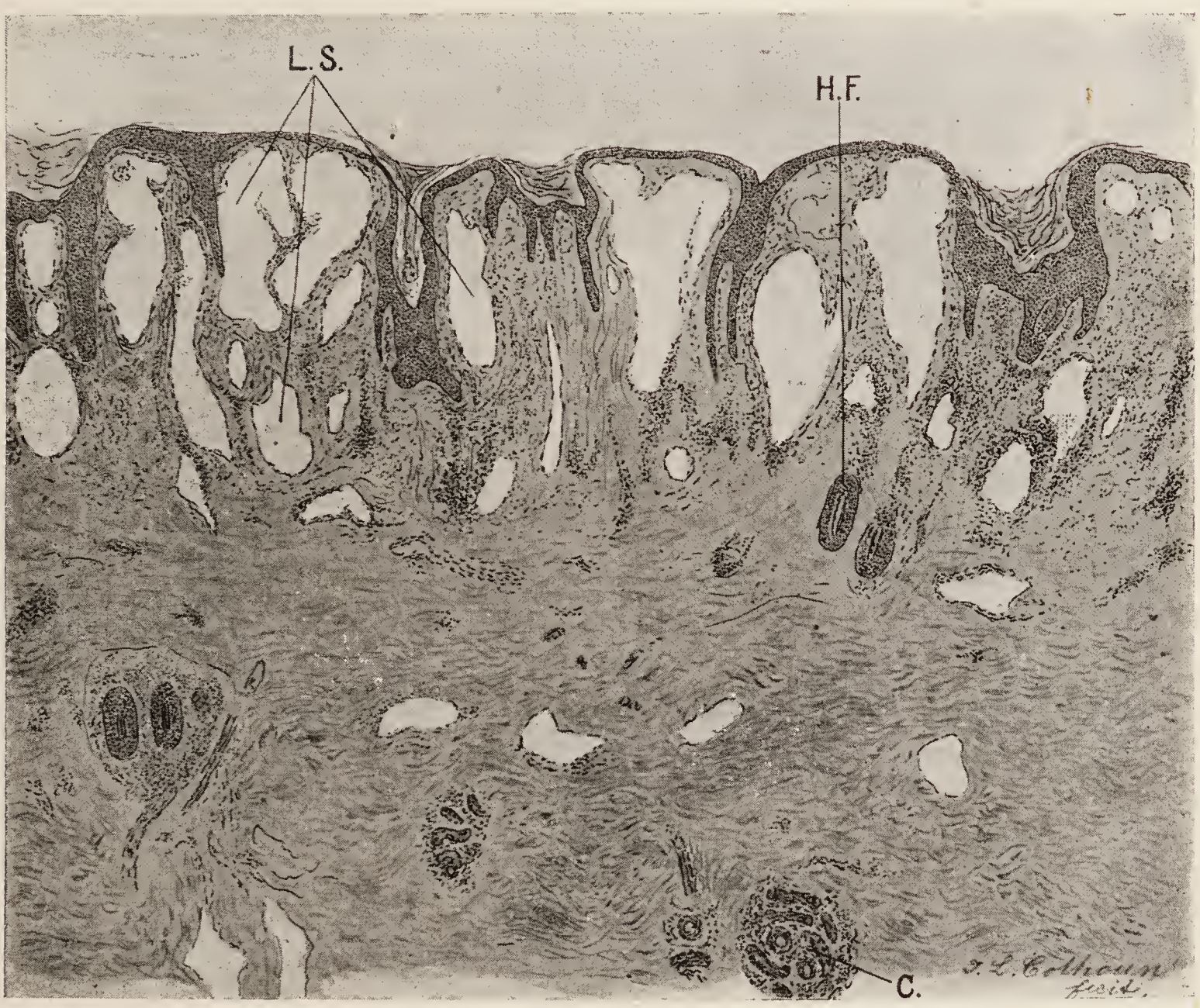

FIG. 35.—Lymphangioma.

L.S. Lymph Spaces. *H.F.* Hair Follicle. *C.* Coil Gland.

the erosion of the wall between a varicose lymphatic and a neighbouring blood capillary. The connective tissue of the central and lower layers of the cutis is normal, that of the papillary body richer in round and spindle-formed cells, and that around the larger cavities often cloudy and glassy, and enclosing colloid fragments. Between the largest cavities and the surface epithelium, there is sometimes no layer of cutis; the lower prickle cells are then partially vacuolised, and there are more leucocytes than usual between them.

Török lays stress on the hyperplastic character of the new growth.

In favour of this, are the close position and more swollen form of the endothelia in the smaller cavities, the occurrence of mitosis in them, and perhaps also the presence of giant cells. He also notes endothelial spaces in the upper parts of the papillæ, where, normally, there are no lymph vessels. Many papillæ contain several such spaces, which are partly in connection with lymph capillaries. The presence of notched processes in many of the cavities is also of importance; they terminate in threads, sometimes contain a cavity, and are to be regarded as endothelial buds. Similar delicate spaces, with commencing endothelial lining, are found, inside larger cell collections, in the surrounding connective tissue; the former indicate homoplastic, the latter heteroplastic new formation of lymph vessels.

I agree with the view of Török, so far as it deals simply with the existence of an endothelial growth. This is proved by the continuous endothelial lining of the larger spaces, as well as by the occurrence of mitosis. The endothelium-clad spaces, however, be they isolated or in connection with the larger cavities, I cannot recognise as convincing proof of a primary endothelial budding of the walls of the lymph vessels. Their occurrence, to which Nasse also refers, may equally well serve the theory of primary dilatation, with secondary endothelial formation. I do not know how a pre-formed lymph space, opening into a lymphatic varix, could look in any way different from these spaces, since the dilatation makes the varix gradually gape from the entrance onwards, and flattens the spindle cells into endothelial form. I apply the same principle to the toothed processes of the cavities; these are only present so long as the latter are not very large, dilated and rounded, and correspond exactly to lymph spaces, which are affected along with the nearest varicosity. Whether the apparently isolated spaces (heteroplastic new formation) are really isolated, and not lateral processes of communicating spaces, further investigation must decide. The greater number of cells around the small cavities, indicates here, as everywhere in the Lymphangiomata, a new growth, one, however, which appears in the surrounding cutis, and, with greater varicose distension of the lymphatics, again disappears. This symptom, as well as the new formation of endothelia, are for me the only, and the only *necessary* signs of a progressive disturbance of nutrition; they justify the definition of Lymphangioma. They are only the results of venous stagnation, and disappear again under the constantly increasing pressure of lymphatic stasis. A connective tissue endothelial budding of the lymph spaces, in the sense of the angioblasts in hæmangioma (homoplastic new formations), I have never observed; nor have I seen heteroplastic new formation of lymph vessels.

(b). *Lymphangioma superficiale.*

On the basis of deeper lying, lymphangiectatic processes.

The lymphangiomatous basis, in these cases, lies either in an error of development or in a traumatic narrowing of the effluent blood and lymph vessels, or it is supplied by an infectious Elephantiasis. The former cases correspond directly to those of Elephantiasis congenita lymphangiectodes; only they develope more slowly, so that they first make their appearance as tumours in adult life, and do not, in general, reach the size and importance of the strictly congenital cases. Among them are the older cases of Gjorgiewicz and Petters-Klebs, and the more recent ones of zur Nieden, Eger and Kast, in which lymphangiectatic processes in the subcutaneous tissue of the leg and labia, gradually affected the skin, and produced, on the surface, vesicular, periodically secreting protuberances.

Bryk has carefully described a very marked case of universal Lymphangiectasis with lymphorrhœa.

> The patient, aged 26, had suffered from childhood from transient swelling of the feet, which, from the fifteenth year, was constant, and associated with severe pain and the formation of small bullæ, from which, from time to time, lymph discharged. Ultimately, an elephantiasic swelling of the feet developed. These were covered with protuberances, sometimes firm and scaly, sometimes soft; when soft, clear or bloody lymph issued from numerous bluish vesicles. On the soles of the feet the vesicles had become confluent ulcers, discharging large amounts of lymph. The swelling of the leg reached to the knee. The inguinal glands formed a tumour of lipomatous consistence, the size of the palm. The left hand and fore-arm were very œdematous, the hand being covered with protruding swellings, as was the right hand, where, however, there was no œdema. On the flexor surfaces of both fore-arms, along the course of the veins, were a few pale nodules, the size of cherry stones, firm, and embedded in the tissue. The patient suffered severely from epistaxis.

At the post-mortem, there was found on the right side a pleural exudation, and in the right pleura a coarse net-work of pretty thick lymphatic vessels. In the posterior mediastinum, a glandular tumour, the size of a goose's egg, had compressed the thoracic duct (from 11 to 2 millimetres); from here down to the groin there were numbers of swollen lymph glands. Teichmann found that all the lymph vessels of the periphery could be injected through the swollen glands. All the lymph vessels of the œdematous arm were very much dilated, their adventitiæ thickened, and they could be followed into the cutaneous infiltration below the nodular vesicles. On the superficial lymph vessels there were, laterally, especially in the region of the valves,

numerous soft, lenticular nodules, whitish yellow on section. The skin of the feet consisted of a convolution of lymph vessels, in a thin, partly sclerotic connective tissue, which in many places was almost completely absent. In the occasional, cystic lymph vessels thrombi were found, and collections of colloid bodies developed from them. The cutaneous nodules were variously constituted. There were some firm connective tissue nodules, of which the younger showed a small cell growth of the blood vessel walls and disappearance of the lymph vessels, the older, scar connective tissue. Then there were simple œdematous nodules with cellular infiltration, in which the convolutions of lymph vessels only reached to the basis, and whose dilated lymph spaces contained reddish serum. There were further, true lymphangiomata, in which, over a subcutaneous, cutaneous and papillary dense net of lymph vessels, there was a vesicular elevation of the epidermis from the swollen papillary apices, and lymph thrombi in the elevated epidermis indicated the course of the lymphorrhœa. Finally, there were hæmo-lymphangiomata of the skin, which had developed by the rupture of some of the thrombosed veins, and filling of the lymph vessels with blood. These bloody nodules were only found at the outermost ends of the extremities, and had given rise to ulceration. In many places the dilated lymph vessels came close together, the walls had given way, and cavernous lymphangiomata developed, or, where the connective tissue had completely disappeared, limited extravasations of lymph, the latter especially in the sub-papillary layer, along with extravasations of blood.

Bryk assumes for these extensive lymphangiectases and lymphangiomata, some congenital hindrance at the opening of the thoracic duct into the sub-clavian vein. This alone would not explain one single peripheral lymphangiectasis, and certainly not this appearance. Here, too, the point of origin is to be sought in the venous system; the mediastinal glands may have compressed the Vena cava as well as the thoracic duct. At any rate, the commencement of the affection with simple œdema of the feet indicates a primary resistance to the outflow of blood, as does the gradually increasing elephantiasis of the legs. But from the time when the vesicular protuberances, *i.e.*, lymphangiectasis, appeared, there must have been a new factor, and this is to be found in the narrowing of the thoracic duct. In this connection there exists, between stagnatory fibromatosis (see p. 832) and Lymphangiectasis with lymphorrhœa, the same relation as between Elephantiasis and the filarial lymph scrotum. The progressive elephantiasic forms indicate a simple resistance to the circulation, the mixed progressive and rarefying lymphorrhœic forms, a simultaneous resistance to the circulation of blood and lymph, while a simple hindrance to the

lymphatics produces neither œdema, nor lymphangiectasis, nor lymphangioma, nor fibromatosis. There are quite analogous cases in adults, in which a congenital basis is of course excluded. I have myself observed such a case of acquired, complicated lymphangioma, of traumatic origin.

> In a boy of thirteen,* following a wound on the back of the thigh, in the second year of life, there had developed, on the under third of the thigh, a cushion-like swelling, the size of half-a-crown, which passed without any sharp border into the neighbourhood, felt doughy, and showed on its surface a number of groups of vesicular, somewhat compressible nodules, some transparent, some covered with firm horny scales. In the centre, corresponding to the no longer visible scar, the nodule feels firm, and the mother states definitely, that soon after the healing of the wound a nodule was noted at this spot ; it only grew to its present size in the last five years. At the periphery and deeper, the tumour is softer, and gives the impression of a collection of cystic spaces, which could be emptied. Some of the vesicular structures contained blood, but most of them a serous, albuminoid fluid. The seat of the growth confirmed the correctness of the etiology, for it differs considerably from that of other lymphangiomata of the leg.

Török investigated a vesicular protuberance from this case, which occupied the space of five papillæ. It was composed of several small confluent cavities, and was continuously lined with endothelium, except on its upper side. The contents consisted of granular coagulated lymph, a few leucocytes, and scattered endothelia. In the neighbouring cellular papillæ, there were found spaces and wide cavities, which, surrounded by protoplasmic, closely-packed endothelia, reached the papillary apices. In other papillæ, the lymph spaces, except for dilatation, were normal. The deeper lymph vessels show no abnormality. In this case also, Török thought it necessary to assume proliferation of the lymphangioblasts, and thus to exclude the simple explanation, that it was due to lymph stagnation. In my view, there was, in this case, a stagnation of lymph, whose effect, in the smaller but not in the larger cavities, was completely compensated by a corresponding endothelial growth, for the latter were not everywhere lined by endothelium.

These two deep complications of the superficial papillary lymphangioma, elephantiasic growth and subcutaneous lymphangioma, are sometimes found combined, sometimes alone, in tropical filarial elephantiasis, and in lesser degree in pandemic streptogenic elephantiasis. On the long thickened skin appear pale protuberances, the size of mustard seeds, which slowly enlarge, and then appear somewhat bluish and transparent. They appear mostly in groups, and

* The case was shown by Dr Leistikow at the Hamburg med. Society. Deutsche med. Woch., 1890, p. 641.

pressure on one will sometimes increase the pressure in another. When the swelling is greater, they run together to larger irregular protuberances, and finally, from delicate tears in the stretched epidermis, lymph exudes (lymphorrhœa). Manson, the scientific discoverer of "lymph scrotum," in which disease this papillary lymphangiectasis is always found, gives no histological description of it. Seeing how frequently the scrotum is removed on account of this affection, thorough investigation with injection of the lymphatics and blood vessels should not be difficult, and promises interesting conclusions, not only on the nature of filarial disease, but also on the mechanism of Lymphangioma and Lymphangiectasis.

B.—*Lymphangioma of the Hypoderm.*

(a). *Lymphangioma tuberosum multiplex* (*Pospelow*).

This form of Lymphangioma is certainly not purely hypodermal, but—as Pospelow's somewhat short description and drawing show—mainly developes in the subcutaneous tissue, and therefore comes close to the other cavernous lymphangiomata, which are all, at first and mainly, hypodermal, and of which only a few extend a certain distance into the cutis. For this reason, and to avoid forming a special class for a single and briefly described case of cutaneous cavernous Lymphangioma, I have placed it here.

> In addition to pigmented nævi, there was found, on the left breast of a girl of twenty-three, a tumour, the size of a pigeon's egg, formed of smaller, bean-sized growths, which had a light rosy colour and a smooth surface. The small growths were isolated on the trunk, neck, and face, elevated over the level of the skin, and, in spite of their firmness, could be caused to disappear by pressure. The size of these single nodules varied between that of a millet seed and a hazel nut. On incision, there was little blood ; in addition to cloudy fluid, there was a colloid mother-of-pearl-coloured substance. The larger tumour was said to be congenital ; the existence of the others was unknown up to the time of examination.

Microscopical investigation showed a loose tissue, beset with tubes and fissures. The largest cavities were in the hypoderm, where the fatty tissue was normal; the smallest, in the cutis, as far up as the atrophic papillary body. They were clothed by an endothelial layer, and contained a quantity of lymph corpuscles.

The case has not, as Pospelow assumes, any resemblance, either clinical or anatomical, to Kaposi's Lymphangioma tuberosum multiplex. That, according to Jacquet, Török and Besnier, was probably a Syringo-cyst-adenoma.

(b). *Lymphangioma subcutaneum solitare.*

The great majority of the solitary subcutaneous lymphangiomata is, strictly speaking, congenital, yet there appear in children and even in adults, quite analogous cases, from unknown cause, or directly following wounds, for which we usually assume a congenital basis. It is remarkable that they especially affect the neck and the upper part of the trunk, the same regions where Lymphangioma superficiale simplex is found. And yet we find, between these two affections, no direct transition, while on the dependent parts of the body, the legs and the genitals, a combination of the deep and superficial lymphangiomata is the rule. No doubt this is largely due to differences in pressure. In the dependent parts of the body, all lymphangiectatic processes have a tendency to expand in the neighbourhood, and to affect the cutis tissue as a whole. The purely subcutaneous forms are met with especially on the neck and the upper parts of the trunk.

They are soft, sometimes fluctuating tumours, of varied size, which are more or less defined from the surroundings, can be shelled out, and extend from the fatty tissue, inwards, along the veins and lymph trunks. On section, a quantity of pure or bloody lymph exudes; they then collapse and show a coarse-pored, spongy structure, and a varying amount of fatty tissue. When they have existed longer, the individual cavities run together to ever larger cystic spaces, and thus form the transition to the purely cystic lymphangiomata, whose cavities can no longer all be injected from one point.

The inter-tissue in the younger cavernous lymphangiomata is soft, cellular and fatty, and contains numerous blood vessels; in the older cavernous and cystoid ones, it is a-vascular, more fibrous, and either delicate and transparent, or denser and firmer. In the former cases it extends into the inner spaces, in the form of septa. In the latter, the cavities are mostly continuously clothed by flat endothelium, and the spaces are united to lymph spaces, which also are lined with endothelium; in the latter case the endothelial growth often does not keep pace with the extension of the lymph spaces, which are then often margined simply by collagenous or fatty tissue. Only where the cystoid transformation has gone on to the development of smaller cavities, and the marginal connective tissue is greatly compressed, are the cavities again continuously lined. Nasse was unable to recognise any excessive growth of endothelium. The cellular infiltration of the inter-tissue appears chiefly around the blood vessels, and consists partly of leucocytes, partly of connective tissue cells; but this requires further investigation with protoplasm stains. Leucocytes certainly do not form an important constituent in Lymphangioma; they are in some cases abundant, but in the majority are

only sparingly and irregularly distributed. According to our recent views on movement of leucocytes, this is no argument against the assumption of a stagnation of lymph.

On section, the cavernous spaces are empty, or contain granular coagulated serum, with a few leucocytes and some fibrinous-looking coagula. The contents are often hæmorrhagic, and contain blood, pure, or mixed with lymph or white thrombi. In such cases, Wegner and Nasse recognised a rupture of the blood capillaries into the lymphatics. Remains of blood and blood pigment are often found in the neighbourhood of lymph cysts, without any occurrence of trauma.

Usually, the fatty tissue is compressed by the extending lymphangioma. At first the fatty lobules are pressed asunder by the lymph spaces; then the cells lose their fat, and partly from them, partly from the thickening walls of the lymph spaces, there is formed a cellular membrane, which shuts off the latter from the rest of the fatty tissue. In this way the lymphatics, which usually surround the fatty tissue, grow into it. But the fat is not always rarefied; in many cases it also increases, and may make the lymphangioma a small part of a mainly lipomatous tumour.

(c). *Lymphangioma of the subcutaneous vessels.*

The dilatation (lymphangiectasis) of the vessels reaching from the cutis to the large inter-muscular lymphatic trunks, appears either alone, or as an accompaniment of a more widespread lymphangioma. It is, in almost all cases, accompanied by a thickening of the wall (eccentric hypertrophy), and may therefore lay claim to the title Lymphangioma. It is found isolated on the leg and seminal cords, along with venous varix, or instead of that, and has the same pathological significance and the same etiology, only an interference to the flow of lymph being added to the hypostatic hyperæmia. Nélaton saw on the lymph vessels accompanying the median cephalic vein, in three cases, ectases 1-2 centimetres long and 3-4 millimetres broad, the result of bleeding scars. More frequent are the varices of the subcutaneous lymph vessels of the prepuce and glans penis, which surround the coronal furrow, and form bands and ampullated dilatations, and then become evident, alongside the dorsal vein, as cords as thick as a thin pencil, which disappear about the centre. Puncture of the vessels leads to escape of pure lymph.

In these cord-like lymphatic varices we sometimes find bead-like dilatations and intermediate constrictions; the latter correspond to still efficient valves. Cylindrical dilatations indicate that the valvular apparatus is overcome; the skin is then exposed to complete stagna-

tion of lymph, and gradually shows the development of papillary lymphangiomata, and ultimately, lymphorrhœa. A very clear case of this nature is described by Thilesen, which may also serve as an example of the combination of this form with wide-spread lymphangioma.

> A patient, age nineteen, had had from the age of one, a painless, smooth swelling, reaching from the knee to the groin, whose volume varied, and which, towards the scrotum, showed a number of vesicular, periodically secreting protuberances.

The patient died of scarlet fever, and the skin of the thigh showed, in all its layers, a distinct hypertrophy. It was permeated by a coarse-meshed net of widespread lymphatic vessels, of which some were as thick as a straw. The most superficial ones could be followed into the vesicular protuberances of the skin, which formed their ampullated ends. The subcutaneous lymphangioma of the trunk had here, without passing on to a subcutaneous cavernous lymphangioma, directly developed into a cutaneous and papillary one. Similar conditions occur in lymph scrotum.

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Lipoma.

In relation to the development of fatty tumours, just as on the development of normal fatty tissue, there are two opposing views, as yet equally likely. According to Flemming, all the connective tissue cells, especially those of the adventitia of the blood vessels of the organs rich in fat, have more or less the power of taking up, from the fatty lymph, one or more drops of fat, something in the same way as they take up hæmoglobin, and manufacture pigment. On the other hand, according to Toldt, certain connective tissue cells have a specific function, something like gland cells, and they alone can produce fat, and are not to be regarded as ordinary connective tissue cells. In favour of this, he mentions the constant freedom from fat of certain areas of the skin, and its early development in others; in short, the apparent independence of the fatty tissue, and of the blood vessel system which supplies it. According to him, then, there are proper "fat bodies,"* which prepare the fat. Certainly, so far as I know, Toldt has not recognised any peculiarity in the cells of his "fat bodies," by which we can distinguish them, before they have taken up fat, from other connective tissue cells, and in this connection Flemming's view corresponds more to our other histological knowledge of the fatty tissue of the skin.

On the other hand, Flemming's view lacks, for pathologists more than for anatomists, something which should explain the capriciousness of the accumulation of the fat, and its preference for certain regions of the skin; in a word, its topography. Some years ago (1882), I endeavoured to supply this by my theory of *the formation of fat by stagnation in the neighbourhood of fat-forming organs*, and I still regard it as the theory which best corresponds with the actual fat formation in the skin.† It assumes no peculiar connective tissue cells at the seat of the deposit of fat in the hypoderm, for I have not found any such, and refers the flow of fat at this place mainly to the activity of the fat-containing coil glands, possibly in a less degree to an activity of the sebaceous glands and the cutaneous muscles, *i.e.*, those organs which separate fatty acids and their products, and introduce them eventually into the cutaneous lymph. Most definite, because demonstratable in many normal and pathological conditions, is the stream of fat which runs from the surroundings of the coil gland to the nearest fat depôt, in the form of fat drops and small, isolated fat cells. This histological fact is the foundation-stone of my theory, and what led me to the idea of the existence of local formation of fat. The second (clinical) fact which confirms me in this theory, is the invariable con-

* Fett Körper.

† And with fat formation in general, which has been little investigated, and is to be ascribed to the activity of the neighbouring muscles, fat glands and intestines. Congress f. i. Med., 1885.

junction of a marked oily hyperidrosis with general adiposity. The great separation of fat in the sweat, recognisable by the strong odour of sweaters, can naturally not be attributed to the fat encapsuled in the hypoderm; but it quite accords with my theory and with the accompanying hypertrophy of the subcutaneous fatty cushion. A series of individual histological facts, which need not here be enumerated, have since then confirmed me in this theory; some of them are found in different places in this book (see Alopecia seborrhoica).

The increased supply of fat alone does not appear to me to be sufficient to explain all the facts in connection with the hypoderm. There must in many, perhaps in most cases be also a *stagnation of fat-containing lymph*. The theory would only be quite satisfactory, if I could prove, histologically, and by the logical estimation of known anatomical and physiological facts, that the lymph in the hypoderm underwent a physiological stagnation, the circulating tissue juice flowing not directly through the lymph vessels in the hypoderm, and only to a moderate degree through the larger trunks which penetrate it, but mainly through the veins of the hypoderm. With the outflow of lymph from the hypoderm,* there is therefore always a combined *filtration of lymph*, and *this* causes the connective tissue cells surrounding the blood vessels to become so rich in fat, that they act as a stimulus to the manufacture of fat on the other *ordinary* connective tissue cells. While consequently, in general, Flemming's view may be thus interpreted, that the *fat from the blood naturally flows first* to the perithelia of the blood vessels, and these therefore produce most fat, these cells, in my view, come first and freely into connection with fat when the tissue juice is *on its way back to the blood*, as a result of phys o-logical stagnation of fat. The ordinary view—so far as it relates not to specific, but not definitely recognisable fat bodies in the hypoderm—regards the normal panniculus, the lipomatosis and the lipomata of the skin, as the results of a pa:·icular activity inside the hypoderm; my theory seeks the explanation of every case either in an increased centripetal flow of fat from the nearest fat-producing organs, or in an increased stagnation of fatty lymph in the hypoderm. Therefore this theory is capable of explaining certain topographical differences, even without the assumption of fat bodies (for example, the want of fat in the eyelids, glans, scrotum, by the abundant supply of lymph vessels) and—whether true or not—it is the only theory which supplies an explanation for certain pathological facts.

Such, for example, is the well-known occurrence of Lipomata on the seat of scars, and on areas exposed to pressure (as in porters), which I have explained as always due to an obliteration of the lymphatics and

* Also with the absorption of subcutaneous injections.

veins, and thus an increased local stagnation of fat; otherwise, so far as I know, there is no explanation of this mechanical development of Lipomata. General obesity owes its origin, according to my view, not to a peculiarity of the blood vessels of the hypoderm which supply to the surrounding cells more fat than to other parts, but to an increased fat-producing activity of the coil glands of the individual.

This must suffice for etiology. But for the position of lipomatosis and the relation of Lipomata to other growths, comes the important result, that they must be removed from the purely proliferative tumours to the group of stagnatory tumours. I cannot more clearly indicate my whole view, than by treating Lipoma, far from Fibroma and Myoma, with the Angiectases and cystic formations, extraordinary as this may appear at the first glance. For, exactly as in Angiectasis a secondary endothelial proliferation succeeds to a primary stagnation, so here, the primary stagnation of fat leads to the secondary production of fat cells.

The main point is whether this new position is supported by histology, or whether it can perhaps even throw a new light on it. For we have specially to keep in mind, that there is not the slightest structural difference between the fat cells of Lipoma and those of healthy skin, such as exists between the connective tissue fibres and cells in Fibroma and those in the normal cutis. All we can say is, that the fat cells in Lipoma gradually become somewhat larger than normal, but that this so varies that it is a very unimportant difference, and explicable by the amount of fat stagnation in the Lipoma. Since the over-fatty cells, so long as they retain their fat, never show mitotic division, in other words the fat cells do not proliferate as such, a macroscopic accumulation of fat can only develope by new connective tissue cells taking up fat, and being added to the Lipoma. Thus we find, when we compare the smaller, recent, and the larger, older lobules of Lipoma with one another, that the vascular septa in the latter have not increased; on the contrary, they are thinner, firmer and less vascular, partly from compression, but also, certainly, from advancing fatty changes in previously unaffected cells, as is shown by the peripheral arrangement of the smaller fat cells in the larger lobules. Ultimately, the rarefaction of the connective tissue goes so far, that many of the smaller lobules run together, and only the larger coarse fibres remain. All the rest of the connective tissue gradually passes into fatty tissue.

This disappearance of the connective tissue, in favour of fatty cells, is a point which does not agree with the assumption of predestined "fat bodies," at least in Lipoma. Toldt's theory altogether is not of much value in pathology. For if only certain cells are destined to become fat cells, and these cannot multiply as such, I do not see how we can explain the occurrence of Lipoma.

As the Lipoma grows, the rule is that the blood vessels in the thinning and sclerosing connective tissue septa also become thinner, retract and atrophy. Finally, only the main septa contain large blood vessels. The capillary net, too, around the individual fat cells, disappears the more these expand. It is only an exception that certain parts of a Lipoma are particularly vascular, sometimes indicating a combination with Angioma.

If the disappearance of the connective tissue does not harmonise with the theory of the "fat bodies," neither does that of the disappearance of the blood vessels, as the Lipoma increases, with the theory of fat deposit from the blood. That would require an increase in the number and calibre of the vessels along with the increase of the lobules.

But the facts completely harmonise with the stagnatory theory, for the blood vessels which serve to remove the lymph—the Lipoma has no lymph vessels of its own—are ever becoming fewer. This permanence of stagnation explains how the Lipoma does not, or only very slightly, diminish in general emaciation. Given a certain degree of cutaneous tension and obliteration of vessels, and the encapsuled Lipoma becomes, with a slight to and fro flow of lymph, a very persistent and absolutely benignant growth. The enormous, colossal forms of Lipoma usually develope because the skin loses its elasticity, hangs down like a bag, and thus the cutaneous tension, which delays the growth, is diminished, while the stasis is positively increased. Consequently, there is further increase of the Lipoma, the tumour becomes heavier, and a further sinking takes place. This *circulus vitiosus* induces, in time, growths of a size little behind the collosal forms of Elephantiasis congenita, which at the first glance do not suggest a simple stagnation as their cause. To me this gradual development to collosal dimensions where physical causes are favourable, on the one hand, and the simple persistence when these are absent, on the other, are in favour of a static cause; at least the true tumours with primary proliferation of the tumour cells behave otherwise.

A theory similar to mine, in relation to development of Lipomata of the skin, has recently been put forward by Grosch. It is similar, in so far as it refers to the topographical distribution and function of the fat-preparing glands (sebaceous and coil glands). But we do not agree about the connection between fat glands and Lipomata. Where there are many glands, much fat is separated, and therefore on these places less fat is deposited, from the blood, in the tissue, than in places with few glands. Thus Grosch explains the frequency of Lipoma on the neck and throat, on the back, and the relative rarity on the chest, the

face, and the extremities. I regard it as possible, that the topographical differences in the distribution of the fatty tissue in the normal skin are due to such differences in the function and distribution of the fat glands, if one at the same time keeps in mind the equally important differences of the outflow of lymph from the different regions of the skin. But in the development of circumscribed fatty tumours, the local restraints to the outflow of lymph, and a consequent greater filtration of fat from the cutaneous lymph, seem to me to play the main rôle,—conditions which are present in scars and regions exposed to pressure.

Grosch would also ascribe the development of the multiple, symmetrical Lipomata to a local altered function of the glands, induced by central nervous influence. I do not think that such a stationary persistent disease can be attributed to central nervous influence. In the only case which I have had long under observation, and in which the symmetrical Lipomata were all seated only on the trunk, I could recognise no alteration in the function of the glands, and no quantitative changes in the sweat and smegma. I therefore believe that even in these cases, while the function of the gland is preserved, the outflow of lymph is here and there, though only in moderate degree, interfered with; the multiple Lipomata never reach such colossal dimensions as the single ones. There is, in the relation to the lymph vessels of the skin to the deeper lying tissues, and especially to the fascia, a series of possibilities of abnormality, which favour stagnation. In my case, the half-crown-sized Lipomata, in their extension and form, correspond pretty much to the swellings in Quincke's acute circumscribed œdema, and, like them, might be related to a single, large cutaneous artery. In the explanation of œdema, lymphangiectases and elephantiasic growths, men have always—wrongly—sought obstructions to the outflow of lymph. They should rather search for such anomalies of the lymph vessels, in connection with the development of Lipoma. Here, too, there is no hindrance and stagnation of the cutaneous lymph as a whole—for this cannot be produced by obliteration of the lymphatics —but a diversion to the outflowing blood vessels of all the cutaneous lymph, in whose resorption an excessive residue of fat is left in the hypoderm.

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Xanthoma.

Under Xanthoma are comprised yellowish-white, yellowish-green, and yellowish-brown, or orange, ochrey yellow, benignant spots and nodules of the skin, which appear either localised, especially on the eyelids, develope very slowly and are persistent; or as a more generalised affection, and then not only on the skin, but also on the mucous and serous membranes. Even yet a series of other benign tumours are, on account of their yellow colour, confused with Xanthoma, most of them hypertrophies of the sebaceous glands, Adenomata, follicular cysts, and also other tumours of the eyelids. Even Lipoma may very closely resemble Xanthoma. Since the time of Addison and Gull, we distinguish, clinically, a plane and a tuberous form. But histologically it is better to separate the entirely localised and excessively chronic form, as *xanthoma of the eyelids*, from the acute, widespread *generalised xanthoma*. For the xanthoma of the eyelid may gradually develope protuberances, without giving up its own peculiar histological character.

Xanthoma of the Eyelids.

These are soft, circumscribed plates, running parallel to the orbicularis muscle, in colour brownish-yellow and somewhat washed out, or light ochre or orange yellow, projecting over the level of the skin, always distinctly in the cutis, and covered by normal epidermis. They are not tender on pressure, and there is usually some general pigmentation of the eyelids.

1. *Xanthoma vulgare of the Eyelids.*

After excluding all incorrectly diagnosed growths, there remain two forms, histologically distinct, of which the one represents the ordinary form, and shows no giant cells; the other is rare, and though not sufficiently separated clinically from the former, deserves, from its containing giant cells, and other peculiarities, special notice.

Where macroscopically only a yellowish streak is visible, we find, microscopically the larger vessels of the skin, especially the veins, embedded in a yellowish opaque mass. Where plates are already formed, there appear, on the other vessels of the papillary body and the walls of the follicles, tumour-like formations, sometimes in the form of cords, sometimes in concentric layers. Ultimately, the whole tissue is occupied by yellowish processes, but even then the predominant character remains a convolution of almost parallel rows of cords. The parallel arrangement depends on the formation of the eyelid, where the thin cutis is only separated from the orbicularis muscle by a very little loose connective tissue. The vascular distribution is therefore very flat,

and the branches run nearly all in one direction. The parallel character is especially marked in the very thin senile eyelids, where Xanthoma is so often present. Here the whole cutis is transformed into perivascular cords, which, separated by large lymph spaces, lie loosely over one another.

It has long been known that the tumours contain fat, to which their yellow colour is due; and the tendency recently has been to ascribe this fat to fattily degenerated or infiltrated connective tissue cells. But the matter is not so simple as with the sebaceous cells or subcutaneous connective tissue cells of the panniculus. Frozen sections, examined in glycerine, show the cords to consist of opaque, badly-defined clumps, of round, oval or irregular form, in which at first no cellular nature is evident, but which, carefully examined, show a very refractile, mulberry-formed surface relief, which is almost characteristic of Xanthoma, and only appears, in a similar way, in fresh sections of Leprosy. The protuberances have a diameter of about 1-2μ, and correspond to small elements, of irregular, rod-shaped, oval, whet-stone or some similar form, into which the clumps at the border readily break down on pressure, and which have a breadth of 1-2μ and a length of $1\frac{1}{2}$-4μ. On the addition of osmic acid, these elements take a brownish yellow, the whole clumps a brown, and finally even a black colour, but much more slowly than the fat of the sebaceous glands and of the subcutaneous tissue, indeed even than the medulla of nerves, while the colour is much more irregular than in these tissues. This osmium reaction is therefore much more comparable to that of the fatty granules of the coil glands. As there, the brownish elements are always separated, and never run together to form large, homogeneous black drops, as in the subcutaneous fat cells and the sebaceous secretion. It is therefore evidently not a mere taking up of fat as in connective tissue cells of the cutis around the coil glands and in the panniculus. Were it really pure fat deposit in the cells, they must have possessed an unusually resistant protoplasmic structure, such as the epithelia of the sebaceous glands, whose spongioplasm long separates the fat drops: indeed it must have been much firmer, for in the sebaceous cells the small drops ultimately run together to larger ones, the spongioplasm being rarefied. Further, it may be noted at once, that there is no preliminary stage, of peculiar hyperplastic connective tissue cells of epithelioid type, to these so-called "Xanthoma cells;" the taking up of fat no more follows the type of the sebaceous cells, than that of the connective tissue fat cells.

Other reactions for fat are, in the so-called xanthoma cells, equally unsatisfactory. A faintly alkaline tincture of alkannin, which instantly stained fresh cells rosy red, with a tendency to yellow, induces no red

colour in these clumps; they remain unstained, or, after some time, take the blue colour of all non-fatty tissue. This alone excludes the possibility that they are fat drops, like those of the panniculus or the sebaceous glands. The reaction with sulphate of nigrosin (elëidin reaction) also fails, yet cyanin gives the clumps a faint colour.

If any doubt exists whether we are dealing with fat, it is instantly removed by warming a fresh section for a moment over the flame. The almost rod-shaped elements of which the clumps consist, at once run together to form drops of the same refractility. If further heated, they gradually run together to very large, readily movable drops, and by continued heating of the preparations, the cords may be quite freed from fat. This fluid fat at once colours red in alkaline alkannin, in osmic acid brown, still, however, more faintly than cutaneous fat generally. The same result was got by observing the removal of the fat, under a cover glass, by ether, chloroform, etc., only the clumps behave quite differently to other fatty cells. If absolute alcohol is run under the cover glass, to dehydrate the specimen, no change appears. But a little ether removes the mulberry appearance; after the ether has evaporated, the clumps appear covered and permeated by bundles of fine refractile needles, which cross at different angles, but in which the individual rods run exactly parallel. The latter are finer and longer than the rod-shaped elements of which the clumps previously consisted. By the further addition of ether, the remains of the clumps, which consist of collections of needles, are gradually dissolved, without leaving any trace. After this removal of fat, just as after heat, the cellular vascular cords of Xanthoma show in their other texture not the slightest change. We never see remains of cells, and never—I most definitely state—do riddled "Xanthoma cells" or "plastin nets" of such remain behind. Indeed, even in preparations hardened in Flemming's solution, in which the clumps usually possess a yellow colour, and their fish-roe form, we may remove the fat from the sections with the same result, that in place of the whole clump, large communicating spaces and passages appear, which correspond to dilated lymph spaces. This is all the more remarkable, as here, in spite of the preliminary stiffness and shrinking of the tissue, the clumps have, in general, taken a rounder, more cellular form, and more justify the customary views.

Treatment of the clumps with fat-dissolving media which can stand water, such as clove oil, anilin oil, also led to solution of the fat-like material.

After all these positive and negative results, so much appears to me to be established, that in the xanthomatous masses we have a special form of fat, which fills the lymphatics in free-lying, com-

municating clumps and cords, and consists of very small elements, twice as long as broad. These elements form, when closely packed, the mulberry or fish-roe-like conglomerations, the xanthomatous clumps, but they are also found scattered all over the tissue. I attribute the change in form, on treatment with ether, to the fact that a more liquid fat is dissolved, and what remains crystallises in the form of needles. This would best explain the half-drop, half-needle form of the original elements, as well as the abnormal colour reactions, which evidently indicate a fat compound, unusually difficult to stain. We get the best view of the so-called fat infiltration of xanthomatous skin, on sections of preparations hardened in Flemming's solution, and dried for a moment on the slide out of alcohol, then treated with a drop of water, and embedded in a drop of gelatine (without glycerine). Every fat granule then shines dark on a clear ground, and after examining such a preparation it is hardly possible to understand how most recent authors regard them as fat cells. (Front., Figs. 18 and 19.)

The assumption of the cellular nature of the clumps is no doubt due to the fact that the nuclei have the type of connective tissue nuclei. But close investigation of the smallest clumps at the periphery shows that this is not invariably the case. The smallest accumulations of the substance in question are fine, elongated, spindle or leaf-shaped; they are simple swellings of the lymph capillaries of the skin. Adjacent connective tissue cells often, but not always, form, with the cells apparently beside them, so-called xanthoma cells. But since the collections usually come into contact with several cells, the protoplasm of which disappears, the smaller xanthoma cells usually show several (three or four), more or less naked nuclei, which at first lie at the periphery. As the lymph spaces become filled and rounded, the cell nuclei pass irregularly into the collections, just as do the naked endothelial nuclei of the large lepra-bacilli clumps. A new formation of protoplasm and nuclei at the periphery, where they often occur, does not take place; true giant cells are not found in Xanthoma vulgare of the eyelids. I cannot regard the large, often gigantic accumulations of yellow fatty substance, with irregular nuclei, as giant cells. Of course a special method is needed to make sure that the yellow clumps are not forms of cells, namely, a method which stains all the inter-cellular substance, and not the substance of the clumps. I would recommend the counter-staining of sections, hardened in Flemming's solution, and stained with a nuclear stain, with water-, or alkali-blue. The yellowish accumulations then stand out very clearly from the bluish ground, and their processes and their close connection are apparent. This "running together of xanthoma cells" has been observed by many,

and is naturally hardly compatible with the cellular nature of the "xanthoma cells."

In fact, we have in the xanthomatous cords, a filling, especially of the perivascular lymph spaces, with a peculiar, very resistant mass of fat, which encloses numerous cellular nuclei. The difference between these and true fat-producing cells is best seen when there are, accidentally, in the section, sebaceous glands or fat cells. The ultimate behaviour of Xanthoma of the eyelids is hardly in favour of the assumption of fat cells, for free fat does not tend to be limited to the cells in which it developes. It is either secreted (coils) or escapes with destruction of the cell body (sebaceous glands) or gradually disappears with nuclear proliferation (fat cell). But the fatty substance of Xanthoma undergoes no change; the cells do not excrete, and do not break down; usually, indeed, the Xanthoma increases with age.

Especially interesting, and against the cellular nature of the xanthomatous clumps, is their behaviour in lepers. There are here found—irregularly, like the nuclei—a few bacilli, and whole clumps of bacilli introduced into the yellowish mass, without the xanthomatous mass showing otherwise the slightest change. How the supporters of the "xanthoma cell" and the "lepra cell" explain this combination, I cannot imagine. The occurrence of xanthoma masses and bacillary clumps in the lymph spaces is a much more natural explanation.

Alcohol preparations show the other characters of Xanthoma of the eyelids. With a good protoplasm stain we find the section abnormally cellular, but the newly formed cells are limited to the cord-like thickenings of the vascular adventitia, which they regularly permeate. They have the type of ordinary spindle cells, with a single, large vesicular nucleus; the protoplasm is often shrunk to a minimum. There are no plasma cells, but the cords contain very numerous mast cells. The interstices between the xanthomatous cords are not more cellular than normal, nor is the sub-epithelial layer of the cutis; but this usually contains in its lymph spaces a considerable quantity of brown and yellow, granular pigment. The basal prickle layer also is often abnormally rich in pigment, and, now and again, but not always, contains fat. The epithelium shows no other changes.

From all this it is clear, that the cellular infiltration of ordinary Xanthoma of the eyelids has not the slightest analogy, not even a distant resemblance to nævus, as has been assumed. Nor does it possess a sarcomatous type. I have a Xanthoma of the eyelid, in which large comedones and sebaceous cysts are present in abundance. This only affected the distribution of the xanthomatous masses, without there being any relation between the two fatty growths.

As to the cause of this Xanthoma, histology may perhaps be a help, since we know that we are dealing with human fat, for the fatty cords are strikingly parallel to the orbicular muscle. If the Xanthoma is deeply extirpated, we see it extending between the muscular bundles, whose processes everywhere run into the tumour. In many places the muscular bundles appear to be compressed by the Xanthoma masses, here and there changing, losing their stripes, and having a waxy appearance, though this is only exceptional. Since I have long derived the fat of the connective tissue from three sources: fatty glands, muscles, and nutritive fat (in the mesentery), it does not appear to me to be remarkable that fat should be deposited on the surface of the orbicularis, just as it is on the surface of the heart. All we require is a weakening of the orbicularis, which may be recognised in many persons, and which leads to a stagnation of fat, for the muscle cannot completely rid itself of its metamorphotic products (just like the heart muscle). These fatty masses are firmer, of a more waxy nature, and therefore less capable of resorption; and this would make it clear why they are especially around the absorbent veins of the neighbouring skin.

2. *Giant-celled Xanthoma of the Eyelid.*

Touton first described the occurrence of true giant cells in Xanthoma, and he noted of them that they were distinguished from other giant cells by the fact, that the nuclei were arranged in a regular circle, around a cloudy centre, and that they were again enclosed by a broad border of protoplasm. This I can confirm from a growth of the eyelid sent to me, with the diagnosis Xanthoma, by Dr Eddowes (London), which contained numerous giant cells. Unfortunately, it was simply hardened in alcohol, so that thorough investigation of the true Xanthomatous masses was not possible, and I could not therefore say whether they were present in the peripheral zone of giant cells, on which Touton lays value. But that it was otherwise quite different from ordinary Xanthoma of the eyelids was clear from the position and the distribution of the cellular infiltration.

While in ordinary Xanthoma of the eyelids, the new formation of cells is arranged in cords around the blood vessels, here it was diffusely extended in the cutis, and commenced directly under the epithelium. The growth was more active in the neighbourhood of the vessels, but this did not affect the regular appearance of the growth. Then the cells were not spindle-shaped, and poor in protoplasm, but rounded, and possessed a large cell body, as to whose structure I was, unfortunately, from the available preparation, unable to draw any conclusion. But there were everywhere present the transitions from these large proto-

plasmic cells to multi-nuclear cells, small giant cells, and finally to very large (Touton's) giant cells, with a homogeneous outer zone. The large giant cells were very abundant, and were regularly distributed from the surface of the skin downwards, which alone distinguished them from the giant cells in Tuberculosis and Syphilis. Otherwise there was no special arrangement of the cells from which they developed, neither cord-like (syphilis) nor concentric (tuberculosis).

Finally, there was not a trace of ordinary xanthomatous material, not even so much as may usually be found even on alcoholic preparations of ordinary Xanthoma of the eyelids.

Here I stop; the giant-celled Xanthomata of the eyelids must be followed by a large point of interrogation. They are probably quite another form of growth, a local infectious growth. Further investigations are requisite.

B.—*Generalised Xanthoma.*

The generalised Xanthoma appears either in healthy individuals, and then usually in youth, or it developes as the result of other, especially liver affections, accompanied by jaundice and glycosuria. This form has its seats of predilection on the elbows and knees, then on the heels, palms and soles, and the genitals. But this usually tuberous eruption may affect the whole body and even the mucous membranes, conjunctiva, gums, œsophagus; further, the peritoneum, endocardium, and the intima of the larger vessels. It rarely invades the eyelids.

In contrast to Xanthoma of the eyelids, the generalised Xanthoma developes from underneath, into the skin, is harder, and usually tender on pressure: it is more sharply defined from the surroundings, and sometimes spontaneously disappears.

But it is mainly distinguished histologically, and so absolutely, that it would be advisable, even clinically, to use another name. We have here, not a persistent infiltration of the vascular adventitia with xanthomatous material, but at first a series of solid, cellular nodules in the subcutaneous tissue or at the lower margin of the cutis, which gradually extend towards the surface, and in their centre undergo fatty degeneration. Unfortunately, I have only osmium preparations of this form; a tuberous Xanthoma of the elbow, which I owe to Dr Pollitzer of New York, and a glycosuric one, which I owe to Dr Robinson, New York.

The two preparations are so similar, and so different from ordinary Xanthoma of the eyelids in all their main points, that I am fully warranted in separating the generalised Xanthomata (including the glycosuric) from Xanthoma of the eyelids, and justified in regarding them as a common type.

The nodules develope in the depths of the skin, or at the subcutis margin; sometimes the coil glands are passively enclosed in them, but

they neither give rise to them nor show any changes. They consist of a rounded accumulation of large, round and spindle-shaped connective tissue cells, which are surrounded by firm collagenous tissue, and are concentrically arranged. The young cells of this nature, which we see at the periphery of the smallest nodules, are very large and protoplasmic, rounded or polygonal, and have a large vesicular nucleus, almost always central. Its place is sometimes occupied by a mitosis, more rarely by two adjacent nuclei; I have not found multi-nuclear or giant cells.

Towards the centre, even of the smallest areas, these cells distend the protoplasm, and show a reticular structure, just as in the sebaceous glands. The nucleus remains in the centre, and from it to the periphery of the cell stretches a delicate spongioplasm, in whose meshes lies a fatty substance, blackened in the ordinary way by osmium. Since the fat drops are ever extending and uniting, the spongioplasm of the individual cells at first tears, while the nucleus diminishes; then the cell walls give way, and the fatty contents of the cells run together in the centre of the area, to a fatty cavity, whose septa consist of the remains of the cell walls, thus following the type of the sebaceous, not of the subcutaneous fat cells. They also resemble the sebaceous glands in this, that in different parts of the area the fatty change extends in varying distances, towards the periphery, so that in the larger nodules the peripheral cells, of elongated and spindle form, are sometimes purely protoplasmic, and then resemble sarcomatous spindle cells, and sometimes fattily degenerated, when, on account of their smallness, they contain only a few fat drops.

Here we have everything which we missed in Xanthoma of the eyelids, and the reason why we there disapproved of the expression: xanthoma cell. We have the original protoplasmic mother cell, the always central nucleus, the spongioplasm uniting nucleus and cell mantle, and the fat drops showing the ordinary osmium reaction; we observe the enlargement and the running together of the latter, the bursting of the cell, and finally no connection of the fatty change with the centre of the area—all copies of the physiological type of the sebaceous glands. Were the epithelial growth and the fatty change to go on in these, after closure of the outlet, which they do not, we would certainly find at the periphery of the sebaceous gland the same fat-containing spindle cells as here.

Independently of the protoplasmic mother cells and their type of fatty change, there appears to me to be. a certain hypertrophy of the collagenous tissue at the periphery of the nodule, and, after they have run together, in the septa of the growth. The description which Robinson gives of his case of diabetic Xanthoma corresponds exactly with my statements on Pollitzer's, only—perhaps on account of the

acuter growth of the glycosuric Xanthoma—the areas were more scattered, with small out-posts at the periphery, and did not there appear so compact and concentrically arranged as in the Xanthoma of the elbow. The main element, here also, was large cellular areas, with no special relation to the vessels, and which underwent a central fatty change.

In view of my scanty material, I would rather say no more of the ordinary form of generalised Xanthoma. It is sufficient to have proved that it is quite different from the ordinary Xanthoma of the eyelid, which alone shows the histological elements which one may call "xanthoma cells."

There are, however, certain cases of generalised Xanthoma which, in their clinical and histological character, are so outside the others, that we must briefly refer to them, if only to warn against confusing the sufficiently difficult question of Xanthoma by too great a leniency in this connection.

Balzer has described a form of Xanthoma in which the elastic tissue formed numerous large coils, which were specially collected around the follicles. The elastic fibres were thicker than normal, and some of them were regressive, fragmented, and swollen. These elastic nodules formed the greater part of the whole growth. Besnier therefore speaks directly of an *elastic Xanthoma*, as a special form. Payne also has recently described a case of generalised Xanthoma, in which there was a great abundance of elastic fibres, but regards it as only relative to the atrophied collagenous tissue; his description otherwise does not exactly correspond to that of Balzer. Now that we possess much better methods of elastic staining, and are beginning to know more precisely the history and distribution of the elastic tissue in the skin, Xanthoma hyperelasticum requires strict confirmation.

Some time ago, I had the opportunity of observing an isolated case, of great clinical and histological interest. Since it will be fully published elsewhere, I must limit myself to a short sketch.

> There appeared on an old woman, on the inner side of the left thigh and the abdomen, hard spots, which, in the course of some years, had distinctly enlarged in extent and depth, and had been variously diagnosed, even as leprosy. Since, on the one hand, the pure xanthomatous colour appeared under the diascope, and, on the other, the whole anterior and lateral parts of the neck, as well as the four eyelids, were diffusely occupied by a smooth, soft, not very pronounced, but still characteristic, ordinary xanthoma, and finally since on the leg there were small xanthomata inside large scars, I diagnosed a variety of Xanthoma which may be described clinically, as *Fibro-xanthoma* (or Xantho-scleroderma) *multiplex*. The areas on the abdomen had about the consistence of thick leather; the patch on the anterior surface of the left thigh was almost cartilagenous at its border, and was surrounded by an inflammatory redness. The sclerosis and the xanthomatous change permeated the cutis throughout, and the central parts

of these surfaces showed a great tendency to necrose, either spontaneously or under various applications. The ulcers which developed resisted all treatment ; at their bases and borders there was simply an indolent, non-granulating xanthomatous tissue.

I then excised a piece of skin from the neck, and recognised the typical appearances of xanthomatous infarction, as I have described it of the soft Xanthoma of the eyelids. Thus the diagnosis of a variety of xanthomata was established. Pieces excised from the large sclerotic part seemed first like a giant-celled Xanthoma. The very large and numerous giant cells, with their dense nuclear zone, contained in their interior no xanthoma masses, but were rather embedded in them. The ordinary fish-roe-like, osmium-browned mass was found compressed between the walls of the large lymph spaces and the giant cells, which were partly marginal, partly free ; it surrounded the latter on all sides, and extended directly from here into a diffuse, nucleated xanthomatous infiltration of the spaces of the whole cutis. In alcohol preparations, where the cutis was partly dissolved, the giant cells lay free in large connective tissue spaces. There was marked hypertrophy of the collagenous tissue, by which the xanthoma masses were closely enclosed, and to this was due the peculiar hardness. The histological diagnosis was consequently *Fibro-xanthoma* (or Xantho-scleroderma) *giganto-cellulare multiplex.*

In view of this case, and those giant-celled Xanthomata of the eyelid, above noted, the parasitic nature of certain Xanthomata is to be suspected, and they may be infectious growths. But for the present, I have, on account of the ordinary form of Xanthoma of the eyelid, which simply represents a xanthomatous lymphatic infarct, ranked them with the stagnatory tumours.

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Urticaria Pigmentosa.

While ordinary Urticaria is a pure angioma, without any persistent histological sub-stratum, the two forms, of Urticaria pigmentosa (Sangster), and Urticaria necrotica (Besnier), are primary, persistent, trophic disturbances of the skin, the one progressive, the other regressive in nature. The name Urticaria is only applied, because, on the basis of the persistent disturbances of nutrition, internal and external irritants may excite a whealed Erythanthema, a so-called Urticaria factitia, or an acute circumscribed œdema, and these appearances have been incorrectly regarded by many as the main and primary factors. The clinical fact, that the eruptions never change their place, should have been enough to show that here, all along, deeper structural changes were present in the skin. Since this has been proved by histological investigation, the affection should, clinically as well as anatomically, be removed from Urticaria, with which it has only one single striking symptom in common.

> The affection developes in earliest childhood, persists to about the time of puberty, and then almost always spontaneously disappears. The spots are dark brownish red, round or oval in form, and are distributed at pretty regular distances on the chest and extremities, in less degree on the neck and face. At the acme of the eruption, probably during the period of detention, the spots are distinctly papular ; as the disease disappears, they become flat. We may distinguish two forms, the coarse and the fine. The former always shows less numerous spots than the latter, in which the body looks like a leopard's. The smaller spots correspond almost exactly to the plane elements of the skin, the larger are double the size or still larger, and less circumscribed than the smaller. On scratching with a blunt instrument, we see that the autogram which developes is, on the spots themselves, a streaked white wheal, while the part of the spot which has not been irritated remains dark red. On the healthy skin between the spots, there is a rapidly disappearing erythema. The wheal lasts unusually long, the erythema often radiates beyond the margin of the spot. Similar, but much less characteristic vasomotor appearances (flat erythema, urticarial erythema, vesicular formation) are seen on the spots, along with spontaneous itching, for there is, in general, scratching of the skin. So far as pigment is deposited to form the brown spots, there is then a localised urticarial autogram.

After Thin had first recognised in this affection, a sub-epithelial accumulation of cells, which he regarded as lupoid, G. and E. Hoggan found, simultaneously with Colcott Fox, that the papule was seated, like a cap, on the almost normal connective tissue of the cutis, and consisted of an almost purely cellular accumulation, in a very fine, rarefied connective tissue frame-work. While Fox found nothing specific in these cells, and attributed the œdema of the wheal to the lymph spaces between them, the Hoggans looked on the cells, on account of their regularly large form and transparency, as something

distinctive, and regarded them as peculiarly œdematous, and as the causes of the œdema of the wheal.

Distinctive the cells are, but they are not œdematous in the sense of these authors. It was reserved for me to discover, what anyone working with recent methods would do, and it has since been confirmed by everyone, that these cells are very large, flattened mast cells. They lie, distending the papillary body and flattening the epidermis above, closely packed, mast cell to mast cell, and are arranged into columns by the persisting collagenous tissue, between which, when spastic œdema is added, wide lymph spaces open. In contrast to Urticaria proper, which shows the œdema through the whole skin, and especially along the large blood vessels (see Urticaria), the white wheal here consists in an œdema limited to the papillary body.

Apart from their cubical form, which is due to mechanical causes, the mast cells show nothing unusual. But they are not, as I believed in 1887, emigrated wandering cells, but, as after-experience has taught me, they have developed, locally, from the connective tissue cells, which take up mast cell granules. All other wandering cells, especially polynuclear leucocytes, are absent, even in the irritated spot.

So far as the accumulation of mast cells reaches in the papillary body, there is found in the basal prickle layer a considerable accumulation of ordinary epidermic pigment, which produces the brown colour of the spots. There is no pigmentation of the cutis; the case of Pick by no means proves that. From the affected child, a light yellow papule was excised with pincette and scissors. Pick found very large, hæmorrhagic areas in the cutis, and therefore believed that the pigmentation proceeded from prolonged hyperæmia and hæmorrhagic exudation. But such hæmorrhages as Pick figures, shine bluish-red through the skin, while the growth in question was light yellow. Pick even says repeatedly that the yellow colour is the last appearing tinge, and yet, in this last stage, a "hæmorrhagic exudation" is visible! The hæmorrhage was simply caused by the scissors and pincette, and the views he founds on this case, which contradict the observations of all other authors, should not be further quoted as correct. Pick's name, Urticaria perstans hæmorrhagica, is therefore utterly wrong.

Apart from the pigmentation and more or less stretching and flattening, according to the degree of papule or wheal formation, the epidermis is not altered. Especially there is no leucocytosis, and no scaling. The appearance of vesicles and blebs, along with erythema from external friction, is probably to be regarded as a partial separation of the whole epidermis from the swollen, and therefore looser papillary body.

In the cutis, we find, around the mast cell areas, slight hyper-

trophy of the spindle cells, and here and there we find one being transformed into a mast cell. But along the blood vessels there is a regular coating of mast cells, right down to the hypoderm, and they show their ordinary spindle form. The blood vessels show no abnormality; neither do the lymph vessels, the collagenous and elastic tissue, nor the follicles and coils.

Consequently the persistent papule may be very simply defined, as an unusually dense collection of mast cells in the papillary body, with accumulation of pigment in the basal prickle layer. The explosive vasomotor phenomena are evidenced histologically as a dilatation of the blood vessels in the whole vascular cone of the skin, down to the papillary vessels, while the skin is made anæmic by a papillary œdema, limited to the mast cell region.

This specific relation of the mast cells to this affection has been recognised by all recent authors (Elsenberg, Raymond, Brocq, Besnier and Doyon, Quinquad and Nicolle). It is opposed only by Doutrelepont, who says that mast cells are also present in abundance in Lupus, tubercular granulations, ulcer of the leg, &c. As a fact, in his case they were not present in the typical arrangement. I could add to these mast-cellular affections of Doutrelepont, a whole series of others (*e.g.*, certain carcinomata, neuro-fibromata, young scars, &c.), and yet this would be no argument against the significance of mast cells in Urticaria pigmentosa. For the specific significance of them is here, rather than in their *constancy* and *number*, in their *arrangement*, the *peculiar, very characteristic architecture* of the tissue, which had been recognised by other histologists (Hoggan, Fox), before they knew they were dealing with mast cells. It would have been better if Doutrelepont had not named his most interesting case Urticaria pigmentosa, for there were neither histological nor clinical grounds for doing so—there was no itching and no Urticaria factitia, but there were thick scales (!) and a swollen serial arrangement of erythematous papules. Both clinically and histologically, Urticaria pigmentosa is a very distinct disease, and it only becomes obscured when such cases as Doutrelepont's are mixed up with it.

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3. *Stagnatory Tumours of Pigment.*

The histology of pigmentary diseases was, up to recently, little considered dermatologically, till the simultaneous works of Aeby and Riehl—in which, for the first time, pigmentation of the epidermis was represented as a function of wandering cells—appeared. The abundant works on pigment which now exist, show very clearly that there was no want of interest in the pigmentary diseases, but only a general confusion, as to how we were to explain and investigate this most important constituent of the skin. The idea of migration of pigment was no doubt a happy thought, which appeared to explain many of the old difficulties; it was at once adopted by the most different observers, and for a time it appeared as if the most difficult part of the work were done. To-day we must regretfully admit that, after all, we are very much where we were, so far as concerns the cause of the slightest human pigmentosis. We are still in the old position; what is the pigment, whence does it come, where does it go? We cannot altogether refrain from regretting that the diligent investigators, who have wrought so laboriously in this field, have made themselves partially responsible for the absolute sterility of their work in regard to human pathology, chiefly because, ignoring other questions in human skin, they have directed themselves entirely to the last and most difficult question, whence comes the pigment? and further, they have sought to get the answer by studying cold-blooded animals. The years of strife between Ehrmann and Jarisch, which all ranged round this question, were useless to dermatology. For to know, from incontrovertible facts, that in many animals pigment is ultimately derived from blood, but in some cases is perhaps formed directly in the epithelium, was really not worth all the quarrel, and only leads us to regret that so much patience and ability were not directed to the pigmentary diseases of man, where they might have borne some fruit. We have first to find some sharp method of distinction between the two different pigments of the skin, the true brownish black, finely granular, epithelial pigment, and the golden yellow, fragmented, iron-containing blood pigment, both of which we daily meet singly or together in our preparations. Then arises the question, whether there are differences between these two, and whether we can artificially produce one from the other? Thus and only thus must we approach the further and most difficult question, whence both come.

With much greater advantage, then, we study the works of those authors, which deal—apart from the skin of the frog—experimentally, chemically and microscopically with human pigment, and only regret that the limits of their work did not permit them specially to investi-

gate, in this way, the pigment in the skin. These are the works of Quincke, E. Neumann, M. B. Schmidt, Nencki, Abel and Sieber, and the older works of Virchow, Perls, v. Recklinghausen and Cohnheim. These we must follow up with better and modified methods, if we wish to part the veil which still hangs over the whole question of cutaneous pigment.

No organ so demonstrates the duality of the pigment as the skin. We see innumerable cases of hæmorrhage, which ultimately leave behind them pigment. Pigment is formed in chronic stagnation, where we may perhaps assume a slow escape of blood-colouring matter, and where we are clinically pointed to a blood stagnatory pigmentosis. But we see on the other hand, without any stagnation or hæmorrhage, pigmentation develope under the influence of sunlight, pregnancy and arsenic, similar to the normal pigmentation of the scrotum, the neck, the breast, and the coloured races, and we see the same melanotic pigment appearing in all pigmented moles and carcinomata.

Have these extreme cases of clinical *Hæmosiderosis*,* on the one hand, and *Melanosis* on the other, been sufficiently examined histologically, as to the occurrence of both pigments? By no means. But this work will only be preliminary to the more difficult one of investigating the nature of the pigment, in those cases where both forms of pigment are present, as in certain infectious inflammations (Ecthyma, Lichen), in the neurotic inflammations (Syphilis, Lepra), and in the senile and marastic skin, etc.

It is not impossible that Schmidt, to whom we owe an excellent work in this connection, is right in considering that the iron-containing pigment of the cutis (hæmosiderin, Neumann) is allied to melanin, and may, in the tissues, pass into it. But this would not explain the striking divergence, under which both appear in the skin, a divergence which most fortunately harmonises with the clinical differences in the two forms of pigment. This harmony is the single definite point in the whole doctrine of cutaneous pigment, and the study of the different pigmentoses must begin here.

Unfortunately, I can only indicate the points which seem to me most promising for the future investigation of pigment, for I have not time to work through the subject myself. But I would at least make it clear why, on clinical and subjective grounds, I divide, for the time being, the accumulation of pigment into the two classes of hæmosiderosis and melanosis. I begin the study by determining in which of these classes any pigmentosis should be ranked.

* See page 960.

Before I conclude these introductory remarks, I must not forget to mention that we must learn to forget a good deal of the recent literature on pigment, for which we have to thank the intimate acquaintance with the pigment of the frog. It has recently become the custom, at first timidly, but now decidedly, to speak of chromatophores of the human skin. If one wishes to apply to every pigmented cell, or every wandering cell which contains a pigment granule, this new name, there is nothing to be said, for it "carries" its pigment with it. But if one refers to the chromatophores of the lower animals, it is necessary to prove that the structures in question correspond anatomically and physiologically to those chromatophores. No one has yet recognised, in the human skin, structures comparable to the chromatophores which serve for the changes of colour; and, until these are found, it is better not to introduce confusion into the question, by the use of a well-defined word of other significance. Nor is it any advance, that since the new era of pigment emigration, all branched pigmented structures of the epidermis have been regarded off-hand as pigment cells. It is not sufficient that one may now and again convince himself of the cellular nature of one of these, but in every single case it is necessary to examine the objects by bleaching and subsequent staining, and to decide whether they are collections of pigment in the lymph spaces, pigmented wandering cells, pigmented connective tissue cells, or pigmented epithelia. But all these questions of transport are secondary to the immediate and important one of the histological (and chemical) constitution of the different cutaneous pigments.

(aa). *Hæmosiderosis.*

By hæmosiderosis I understand—in contrast to melanosis—all those pigmentations of the skin, in which the pigment shows iron-containing granules, showing Perls' and Quincke's reaction. It is by no means necessary that all the pigment granules should give the iron reaction, nor that the reaction should be recognisable in every stage of the affection, but it must appear some time, and at some stage of the process. If it is never present, we are dealing with a melanosis.

This definition guards us from a too hasty identification of the hæmosideroses with hæmorrhagic pigmentations, which certainly all belong to the hæmosideroses. In the first place, in most of the distinctly hæmorrhagic processes (hæmorrhages, stagnatory dermatoses, pigmented sarcoma), the definite recognition of the iron stage in the pigment is not successful, and probably many pigmentations belong to the hæmosideroses in which neither clinically nor microscopically can a hæmorrhage be recognised.

On the other hand, the reason why we must be content with the *simple qualitative* recognition of iron *at some stage* of the affection, lies in the behaviour of the iron reaction in the most typical hæmorrhagic pigmentations. Neumann first pointed out that the pigments distinguished by Virchow and Perls, the iron-free hæmotoidin and the iron-containing pigment, are not formed at the same parts of the tissue, but that the latter requires the aid of living tissue for its development. In thrombi, Neumann found the hæmotoidin in the thrombus, the so-called hæmosiderin in the tissue around. Then Schmidt recognised, that even in living tissue, the iron reaction is not always present, but only developes gradually, and may again be lost. It forms then only a stage in the regressive metamorphosis of hæmoglobin. According to Schmidt, the change is the following: the hæmoglobin separates in drop form from the stroma of the blood corpuscles, then, both free in the tissue and inside the cells, is transformed into golden yellow, shining granules, while the eosin reaction of the hæmoglobin drops is lost. While the granules then become reddish brown and less bright, the iron reaction appears, and is greater, the more marked the brown colour of the granules. Finally, the coarse brown granules break down into finer ones, and the iron reaction is again lost. Schmidt believes it is possible to follow this experimentally produced series of changes directly to the brownish black, finely granular melanin.

These changes form a good foundation for the discussion of the hæmorrhagic dermatoses. An excellent object on which to study them, at least at their acme, in sections, is the pigmented skin of the leg, in the neighbourhood of varices, and especially where scarring has taken place. In the pigmented scars of ulcers of the leg, from a body otherwise poor in pigment, especially above thrombosed varices, we have ample reason for assuming a hæmorrhagic pigmentosis, even if the emigration of hæmoglobin into the tissue is long past. Especially one preparation, in which, on every section, a thrombosed varix was found in the subcutaneous tissue, provided me with specimens, which, as a whole, completely confirm Schmidt's statements. Here the cutis, in its whole thickness, was so densely permeated by golden yellow and yellowish brown granules of pigment, that one might almost describe it as a pigmentary injection of all the lymph spaces of the scar; the flat, atrophic epidermis above was also deeply browned. Inside the thrombus, in an almost concentric semi-circle, were hæmotoidin crystals, a proof that blood corpuscles had here given up their pigment.

In this typical case of hæmorrhagic pigmentation of the skin, the iron reaction gave the following results: — the hæmotoidin crystals remained, as was to be expected, unaffected, as did all the

epidermic pigment. But all the pigmentary infiltration of the scarred cutis gave the blue reaction with yellow prussiate of potash and hydrochloric acid, the black with sulphide of ammonium. Inside every collection of pigment there were, however, some granules which stained faintly, and others which did not stain at all, and these were, as Schmidt states, especially the light yellow, shining granules, those which were in transition from hæmoglobin to hæmosiderin, but already had the form of true pigment granules. But there were no transition forms from hæmosiderin to the pigment of the epidermis, showing the typical dark brown colour, and the fine, irregular, partly angular form of the melanin of negro's skin and pigmented moles. Neither were there, in the cutis, coarse, dark brown granules, which did not give the iron reaction, nor was there a breaking down of the hæmosiderin in the cutis, into a brown pigmentary dust, resembling epidermic melanin. Nor were there transport cells, which, lying at the dermo-epidermal margin, aided a transition between the two pigments. The cutaneous pigment was found, just as Schmidt says, partly inside the spindle cells, partly outside, but this made no difference to the iron reaction. But we must admit that spindle cells, which were not particularly abundant, and contained little protoplasm, and whose size would not have been sufficient to conceal all the pigment, appeared to act as attraction centres of the pigment, for the neighbouring lymph spaces were particularly rich in it. In the atrophic epidermis of the scar, leucocytes and pigmented spindle cells were altogether absent, and the pigment here lay, partly inside the basal prickle cells, surrounding the distal poles, partly in the inter-epithelial spaces. If then a transportation of pigment to the epithelium had taken place, it was solely by means of the lymph stream.

There was thus seen, in a case in which clinically there was certainly hæmorrhagic pigmentation, and the escape of hæmoglobin was histologically recognisable, a pigmentation in the epidermis, apparently completely independent of the excessive cutaneous pigment, and which, microscopically, had all the characters of melanin. That a whitening, atrophic scar epithelium should form pigment is incredible, and so far as I know has never been suggested. It must then have got its pigment from the cutis, and yet in none of the sections was there evidence of transport, or, what is still more important, any transition forms. The question of the eventual connection of the two pigments can nowhere be more precise than on this preparation, and I therefore recommend it to future investigators.

My next aim was to obtain, in this specimen, further reactions for the recognition of hæmosiderin in the cutis, and melanin in the epidermis, and I asked Dr van der Vegt to undertake the research. He

found that the cutaneous pigment gradually and completely dissolved in strong hydrochloric acid; previous to this the iron was all gone, as was shown by the negative iron reaction. But in sections thus treated, the epidermic pigment was unaltered, and did not show, after the acid, any secondary iron reaction. In a weak potash solution of peroxide of hydrogen, it was however completely dissolved, whilst, similarly treated, the cutaneous pigment not only persisted, but even became darker.

In a second case of pigmented scar from a varicose leg, the reactions of the pigments were the same.

Of course this material is far too small to decide such an important question as the independence or the relation of hæmosiderin and melanin. It only seems to me that the lucky choice of this object allows certain conclusions to be drawn. First, it is not conceivable, that, in the case in question, the melanin was directly removed from the blood and deposited in the epidermis. Were this so, it must have been, like hæmosiderin, met with somewhere in the cutis, and would certainly have been visible after the destruction of the hæmosiderin with hydrochloric acid. But the melanin could not arise directly from the hæmosiderin, for then we would have found, in the cutis or the epidermis, some transition between the pigments, in colour, form, or reaction, instead of which we find nothing but the most marked distinctions.

But since the pigment of the scar epithelium in this case cannot very well have come from anywhere else than from escaped hæmoglobin, it must have been conveyed to the epithelium in an unpigmented form, and precipitated inside the epithelium as melanin; just as from the matrix in thrombus, only hæmotoidin, in the scarred cutis, only golden yellow, fragmented pigment and hæmosiderin are found. It is seen, then, that this preparation leads me to a further enlargement of Neumann's theory, according to which *the nature of the locally developed pigment, even from the same source, depends on the soil in which it is formed, and therefore shows in the epithelium other forms and chemical composition than in the cutis.* Considering the very different chemistry of these epithelial layers, such an incongruity is not remarkable. Investigations by Dr Heuss in my laboratory showed, in the uncornified epithelium, a distinctly acid reaction, and in the lymph spaces of the cutis, a faintly alkaline one; in the neighbourhood of the horny layer, marked reduction processes, in the neighbourhood of the blood vessels, oxidation processes. Thus we see that the cutaneous pigment is sensitive to hydrochloric acid, but not to a weak solution of potash. For it was surrounded by a weak alkalin lymph while it was being formed, and since this removes the special acid con-

stituents from the matrix, it increases the reaction of the cutaneous pigment to acids. The melanin of the epidermis, on the other hand, is formed in acid surroundings, and under the influence of reduction processes, and therefore shows itself sensitive to alkalis and oxidising agents. If we follow this out, it appears possible that we may meet, at the margin between cutis and epithelium, with an amphibolic, transitional pigment, without this being a proof of the transport of fully formed cutaneous pigment into the epidermis. But in my preparations none such is seen; there is nothing but the sharpest distinction. But since the difference in chemistry, between epidermis and cutis, ultimately depends on the histological difference, that we have in the one large masses of protoplasm and no blood vessels, and in the other little protoplasm, abundant oxygen and alkalin blood serum, it is conceivable, that in cases of greater accumulation of protoplasm in the cutis, melanin may form, *along with* hæmosiderin, without this being a proof of a development from hæmosiderin. Thus I would explain the observations of Schmidt (on Sarcomata), which he applies to the theory of the direct transition between the two pigments.

I can thus distinctly place among the hæmosideroses: the pigmentations of the cutis after hæmorrhage, in chronic stagnations of different forms and in sarcomata, and those in ulcerations and scars (in white people). The pigmentations in certain acute (Cantharidin, mustard) and chronic dermatites, are questionable. Every single object needs to be thoroughly examined.

(bb). *Melanosis.*

The melanoses comprise all those pigmentations of the skin, in which there is never any iron reaction of the pigment recognisable. But since, on the one hand, the numerous dermatoses of this class are very rarely carefully tested on this point, and on the other, as in several of them, there are contradictory statements as to the presence of iron, we must wait for fresh investigation and perhaps better methods of the recognition of iron, before definitely defining this group of skin diseases. For the present, its position must depend on the principle, that it shall include all pigmentary diseases, in which the presence of iron is not certainly demonstrated. One single positive statement as to the presence of iron, as we have of Addison's disease, can hardly hold against the almost unanimous negative results of after-investigators. But it is conceivable, and to be hoped, that further improvements in our methods will teach us positive differences, by which we shall be able to break up the large group of melanoses, at present

united simply by the negative iron reaction, into smaller and less evidently mixed sub-sections.

A rational division of the melanoses can, at present, only be based on certain pathological changes, and I believe that it is best to distinguish three groups, according as the pigmentosis is due to the external irritation of the chemically active rays of the sun, to toxins circulating in the blood, or finally, to reflex action from other organs.

The first group, of the *actinic melanoses*, comprises, in addition to a few skin diseases, a series of completely or almost completely normal pigment changes; very naturally, for the attraction of pigment under the influence of light is a great remedy in the economy of nature; it everywhere serves, more in the lower animals than in the higher, to preserve the eye or the skin from external dangers. Lutz has told us, that this pigmentation is a persistent active function in the dark races, entirely dependent on the influence of light, for their skin is bleached under plasters which do not permit the passage of light; that the children of coloured parents—in spite of Morison's statements—are born light, and that the pigment present in their skin only appears under the influence of day-light, either becoming darker or reaching nearer to the surface. And the very interesting periodic changes of colour in a Kaffir, which Niemeyer observed, concerned almost exclusively the exposed parts of the skin. If we wish to be sure as to the nature of the skin diseases which come under this category, Ephelis, Sailor's skin, Xeroderma pigmentosum, and Blue pinto, it is especially necessary to study the normal pigmentation of the dark races in their physiological conditions, under the influence of sun-light, more thoroughly than has hitherto been done. The only fact which I have to bring forward, is, that the pigment, which was abundantly present in the upper cutis of a blackened scar on a negro, showed no iron reaction. As the pigmentation of Xeroderma pigmentosum and sailor's skin has already been described in the chapter on carcinoma, there remains to us only the discussion of Ephelis and Pinta cœrulea.

Much less defined than this group, is the second one, of the *toxic melanoses.* Here the position of the individual dermatoses is doubtful, partly as regards their position under melanosis generally, partly as regards their being looked on as toxic melanoses. While, for example, the melanotic nature of the pigment in Addison's disease may be regarded as pretty certain, many authors ascribe the deposit of pigment rather to reflex action from the supra-renal bodies (corresponding to the formation of Chloasma in pregnancy), than to a circulating poison. This view will hardly stand for those pigmentoses which accompany Syphilis and Leprosy, although here a nervous influence in the symmetry and other clinical peculiarities, is undeniable. But that at least the reti-

cular depigmented syphilide is a true melanosis, I have most definitely convinced myself. Here we would include also the pigmentations due to the internal use of arsenic, and perhaps also senile hyperchromatosis. To the toxic melanoses, we have also to ascribe, as a local form, the *Tâches bleues ou ombrées* of the French authors.

The third group, of *reflex melanoses*, is the smallest and most obscure, but perhaps destined to be the most interesting, for it is open to animal experiments. It is an old experience, that, under the influence of pregnancy and different affections of the genitals, in people not entirely fair, several parts of the skin, especially the nipple, linea alba, the skin of the face, and even moles take on a deeper pigmentation, which, after the removal of the cause, again disappears. We call these reflex and transient, mostly widespread and diffuse, but usually regionally limited pigmentations, Chloasma, and distinguish them sharply from persistent pigmented moles and lentigines on the one hand, and from the ephelides which arise under the influence of external light, on the other.

In addition to these acquired melanoses, there is a large group of congenital melanoses, the pigmented nævi, which we will consider under malformations. With these I reckon also the smaller pigment moles, which are called Lentigines, and are often erroneously confused with Ephelides. The group concludes with the pigmented carcinoma or melanoma, which we have already described under nævo-carcinoma.

($\alpha\alpha$). *Actinic Melanoses.*

Ephelis.

Ephelides are collections of discrete, peppercorn, round or irregularly margined spots of pigment, which appear, in youth or middle life, on parts exposed to the light (face, neck, arms, backs of hands), and are evidently dependent on sunlight. They never show, like Lentigines and pigmented moles, any elevation over the level of the surroundings, and a brownish black colour, and never, like Chloasma, a band-like form and diffuse extension and confluence.

From the investigations of M. Cohn, the pigment in ephelis has the same distribution as on the more deeply pigmented spots of the normal skin of white races. It lies mainly in the epidermis, in whose deeper layers it is both intra- and extra-cellular, and has the properties of melanin. In the cutis only few pigment cells are found, and these in the neighbourhood of the vessels. Enclosures of collections of embryonic epithelia, and hyperplastic vessels, such as are found in pigmented nævi, are never present.

I have had the opportunity of examining three cases of Ephelis; one from the face, two from the arms. The appearances were just as Cohn describes. There was always a deep pigmentation, limited to the

region of a few papillæ, of the undermost layers of the prickle cells, with a melanotic pigment, which showed no iron reaction, in which they resembled the few free pigment granules and the pigment cells of the papillary body, near the epithelial margin. There were no pathological changes in the vessels, and no distinct relation of the pigment to the vessels. This should have been most apparent on horizontal sections, for the spot of pigment might perhaps show some relation to the circulatory plane elements of the skin. But I could not discover it. The cause of the grouping of the Ephelides, their limited extension, and the complete absence of confluence, is unknown to me. In two cases the cutis showed a widespread transformation of elastin into elacin, especially in the central part.* But these altered areas did not exactly correspond to the pigmented ones, and since the skin came from middle-aged individuals, I would not relate it to the pigmentary changes. It is rather possible that the skin which answers to light with this alteration of pigment, is perhaps altered in its elasticity for the same reasons. These pieces of skin contained the same scattered cellular areas as senile skin, a symptom not proper to Ephelis as such.

Pinta cœrulea.

Pinta cœrulea of the Mexicans is, according to Lier, a congenital anomaly of pigmentation, an imperfect attempt of the white and mixed races to acclimatise themselves in the tropics by greater pigmentation. Evidently several affections are described in tropical America as "Pinto," and only blue pinto seems to be a pure pigmentary anomaly. I believe that I saw a case in a gentleman from Columbia. He had, on the face, especially on the forehead and temples, collections of dark bluish black points, not unlike the result of a burn with gunpowder, or blue tattooing.

In this case, microscopical investigation of the spot showed a very marked pigmentation of the whole sub-papillary and papillary, somewhat hyperplastic vessel system, while both the deeper parts of the cutis, and the epidermis were almost free from pigment. With a higher power, the upper part of the cutis was seen to be penetrated by fine threads of granular pigment, and these reached up to the basal prickle layer, to end between the cells, or in a very faint pigmentation of the epithelia. But this minimal epidermic pigmentation, especially with a low power, was as nothing compared to that of the sub-papillary vascular net. Here, the pigment lay, especially in hyperplastic connective tissue cells, but often only in masses beside them, so that they were often surrounded by formless fragments of pigment, twice or thrice the size of cells. Leucocytes and "transport cells" for the epidermic pigment were never found.

* Regarding elastin and elacin, see the chapters : Senile skin, Scars, Colloid degeneration, Myxœdema and Striæ.

The colour of the pigment was dark brown, fragmented and finely granular in the neighbourhood of the vessels, and still more deeply browned in the neighbourhood of the prickle layer and inside it. But even immediately around the vessels it never gave the iron reaction, neither with yellow prussiate of potash nor with sulphide of ammonia. Consequently, in spite of the position of the pigment, it was a pure melanosis.

The dark blue colour is explained in this case by the deep seat of the pigment under the surface of the skin, and the almost complete absence of epidermic pigment. Had the latter been present in larger amount, the spot would have had a brownish black colour.

(ββ). *Toxic Melanoses.*

Pigmented Syphilides.

The neuro-syphilides have been partially described, on the basis of Bockhart's and my own investigations, under the histology of the pigmented neuro-syphilide. Here I have shortly to describe pigmented syphilis in general, from the standpoint of pigmentation, after I have referred to the somewhat deficient literature on this interesting question. It all relates to the rete pigmentosum of syphilitics.

> The best work is that of Majeff, which corresponds exactly with my view in recognising the commencement of the affection in a diffuse *increase of pigment*, usually of the skin of the neck. On this yellowish-grey ground, there then appear, *secondarily*, small, scattered *light spots*, while the colour of the rest of the coarse net becomes a *deeper brown*. In a third stage, of decrease, the white spots increase more and more at the expense of the rete pigmentosum, while this also becomes lighter, so that the marked contrast of the second stage disappears.

Majeff examined four pieces of skin, from different stages of the affection. At those places where the skin was dark, he found the prickle layer considerably thickened, and laden with pigment, both in and between the epithelia. The walls of the blood vessels were thickened by increase of collagen and infiltration with "round cells," their endothelium, swollen. They were, especially in the papillary body, surrounded by numerous round, oval, and stellate pigment cells, and there was everywhere free pigment. At the light spots, Majeff found the epidermis thinned in all its layers, even to one or two rows (!), and the nuclei did not stain well. The pigment diminished from the border to the centre of the light spots, where it completely disappeared. The vessels, there, were narrowed and hardly visible. Majeff concludes that it is a chronic inflammation, which commences with vascular change. This leads to disturbances of circulation, with formation of blood pigment. Then the vessels are obliterated, the capillaries are at

first thickened, and later undergo atrophy. At the same time the pigment is absorbed.

Completely in accord with my own experience, is the fact, that in the pigmented zone (without concurrent roseola) there was a cellular infiltration and endothelial swelling of the vessels, but I have not been able to determine, as Majeff did, in the light zone, vascular atrophy, epithelial thinning, and complete disappearance of pigment; mine must have been an earlier and less severe case than his.

Ehrmann makes no distinction between pure pigmentary syphilis and post-papular pigmentation, between neuro-syphilides and syphilides. "A leucoderma without previous macular or papular eruption does not exist." Therefore his general statements are not altogether acceptable. "In the syphilitic papule or macule, abundant pigment is formed in the infiltration cells, and is conveyed in abundance to the epidermis, therefore each spot usually leaves behind it pigment." This statement requires confirmation; I found the pigment in the ordinary papules either unchanged, or, usually, less, even on otherwise deeply pigmented skin, and was able to show that the (clinical) so-called pigment of the healing papules depends on an optical error. In "leucoderma syphiliticum," the branched pigmented cells which, according to Ehrmann, transport the pigment to the epidermis, are absent; the export of pigment is stopped. Then the basal prickle cells first decolourise, followed by the higher lying ones, and finally, the pigmented horny layer scales, and thus the epidermis becomes non-pigmented, while abundance of pigment is collected in the cutis.

Drawings of these different stages of rete pigmentosum would be very desirable; one might then draw a conclusion as to the probability of the paradoxical law, that the pigments collect in the cutis for want of pigment carriers; for most authors, from the clinical side, state that the pigment disappears from the cutis. We have just seen that, according to Majeff, it really disappears, while I still found it, though distinctly diminishing; but I have not suggested that during a presumptive rise to the epidermis it met with a barrier, and stopped.

Ehrmann explains the pigmentation in the growing papules (condyloma ?) differently. "The conditions are altered if the papule grows; then the infiltration of the corium reaches such an intensity, that the formation of pigment ceases. The degenerated epidermic cells may, however, earlier cease to take up pigment. It disappears from the epidermis and the dermis. But the branched, pigment-carrying cells persist for some time, only they cannot convey pigment to the epidermis."

Why should this pigmentation be arrested here, if it goes on freely in the simple papule? What is this peculiar unknown degeneration of the epidermic cells, which deprives them of their power of taking up

pigment? Are there really histological preparations which show the pigment, in a syphilitic papule, in branched cells, only at the margin between epithelium and cutis? Is it probable that, in one case, the depigmentation ensues on account of the absence of bearers, and then at another stage of the same affection, where these bearers are present, on account of a "dislike" of the epithelial cells to the pigment?

Riehl and Jarisch, in rete pigmentosum, take the opposite view of depigmentation, namely, the export from the epithelium into the cutis, and from it onwards. Jarisch connects with this backward transport, the regular presence of cellular infiltration, which he observed around all the cutaneous vessels, even the deep ones. And Riehl found, under the light spots in the cutis, numerous pigment-containing cells.

We see then that there are only two facts certain, the widespread hyperplasia of the endo- and perithelium of the blood vessels, and a diminution of the pigment at the white spots, so that at a certain stage the epithelium, but not the cutis, is depigmented. All the rest is matter for argument, or unknown. We are therefore, in spite of these works, just at the commencement of the matter. We have theories in abundance; what we want are thorough investigations.

Until very recently, in regard to retiform pigmented syphilis, from the time of the works of O. Simon, Lesser and Neisser, the view had been pretty general that the white spots were the important parts of the process, and this general view is shown by the fact that, instead of pigmented syphilis, we speak of "leucoderma syphiliticum." Only recently, through the works of Majeff and Taylor, is there a tendency to turn round and to give to *primary pigmentation* its right and ancient place. I have, from clinical reasons, all along maintained the old view, and my work on neuroleprides and neurosyphilides has only confirmed me in it. In the rete pigmentosum of syphilitics we are not dealing with a persistent depigmentation like Vitiligo, but with an *oscillation of the pigmentation, which commences with a widespread hyperchromasia.* Therefore this affection is *not* a hyperpigmentation, and not, like Vitiligo, a disappearance of pigment, if we consider the essentials of the process. After the retiform syphilide has passed, the patient is, in my experience, just as pigmented as previously; the vitiligo patient is less so. Common to both affections is only the net form of the pigmentation, which indicates in both a vaso-neurotic basis, without assuming that the ultimate fate of the pigment is the same in both cases. As to the net form, I have said enough in the introduction, and in the chapters on anomalies of circulation and neurotic inflammations. Here I have only one thing to add in connection with the primary pigmentation which forms the basis of the ultimate disappearance of the pigment. It almost never developes on completely unpigmented skin;

almost always on the region of the neck, throat and the surroundings of the axillæ, &c., which previously had normally a smoky, greenish yellow colour. If one examines a number of non-syphilitic persons, he will find, that especially younger, thin, insufficiently nourished individuals with pale faces, especially females, show at these spots a diffuse hyperchromatosis. This explains the frequency of the affection in females. Every diminution of nutrition shows the affected spots darker. In the florid stage of syphilis there is such a darkening, and it is always more, the more the partial disappearance of pigment is added. At the height of the affection, the net is therefore much darker than the normal skin of the neck, but the light meshes of the net are not whiter, and usually much less light than the rest of the always unpigmented skin of the body. We have then not a primary and total depigmentation, not a Leucoderma, but a primary pigmentation, which, on definite parts of the skin, is complicated by a secondary depigmentation, leading back to the normal. Neither the pigmentation nor the depigmentation have any necessary relation to syphilitic papules which may be present.

Addison's Disease.

The hyperchromasia of patients with this disease is evident clinically as a diffuse increase of the cutaneous pigment, which first affects the hands, with the exception of the nail bed, the face, the genitals, the borders of the axillæ, and the joints, and gradually gives to the whole body a mulatto-like, irregularly spotted, "bronzed" appearance. Greyish brown spots also appear on the mucous membranes. As a rule, there is no symmetry. Those parts which are exposed to light are usually somewhat browner, the rest of the body more a greyish colour; this depends on the greater pigmentation of the epithelium in the exposed parts.

Nothnagel found the pigment increased, but otherwise in the same form and distribution as on deeply pigmented normal skin (scrotum, negro); it had the appearance of melanotic pigment. He could not obtain any iron reaction, but he believed that the hæmatogenic granules of iron were perhaps in some combination, which did not give the Prussian blue reaction. Perls was able to "blue" the pigment in the cutis, while that of the epidermis remained unaffected. Kulenkampff found, only in the subcutaneous tissue, a few granules which took the blue colour.

Caspary found in investigating the deeply pigmented scrotal skin from a case of Addison's disease, not only pigment cells with long processes between the basal epithelia, but also pigmented connective tissue cells in the neighbouring cutis, which sent long processes between the epithelia, and part of whose bodies reached into the prickle layer. These resembled the radiating pigmented cells of the choroid and iris, but were as different from the non-branched pigment cells lying

deeper in the papillary body, as from ordinary leucocytes. The pigment had not the light yellow colour of blood pigment, but was distinctly darker. Besides being in these inter-epithelial cells, it was also seen embedded in the mantle substance of the epithelia, and surrounding the poles. Caspary drew no conclusions as to the origin of the pigment. The walls of the blood vessels were normal; there was no formation of thrombi, and the surroundings were not distinguished by any abundance of pigmented cells.

v. Recklinghausen found the pigment, as well as in the prickle layer and papillary body, especially around the veins,—a circumstance, which would be in favour of a stagnation of the lye of the pigment during its absorption.

Riehl found, in addition to the same relations of the pigment of the epidermis and the perithelia, a marked multiplication of the cells of the vessel walls, especially of the sub-papillary net, but it was also evident on the vessels of the deeper net. The muscularis of many cutaneous arteries was thickened, swollen and cloudy, its nuclei only stained faintly. In two of the four cases he examined, there were, in many preparations, macroscopic bleedings in the cutis, in one they were completely absent, and in another only sparingly present. Sometimes they surrounded the vessels in the form of circumscribed pools of blood, but usually they occupied diffusely the border between cutaneous and subcutaneous tissue. They never in their extension corresponded exactly to the intensity of the pigment at the place. Some arteries and veins were thrombosed, and hæmorrhages were then found in their adventitia, and there were affections of the walls, without thrombosis in the vessels. It is important that there was no transition stage, of breaking down blood corpuscles and transforming hæmoglobin, between the hæmorrhages and the pigmented cutaneous cells around, nor were there any free fragments of pigment.

These observations of Riehl, which led the author to recognise the origin of the pigment in the blood, and the method of pigmentation, so contradict the statements of other authors, that they cannot be generally accepted; extensive hæmorrhages could hardly escape observation. And the pigmentation of the epidermis was not in proportion to the escape of blood, which, moreover, was completely absent in one case.

This incongruity between the statements of Riehl and other authors, led von Kahlden to investigate the conditions anew. He found the lowest two or three rows of prickle cells deeply pigmented. The pigment often filled the basal epithelia so completely, that the individual granules, as such, and the nucleus were obscured, but the nucleus was never pigmented. Sometimes the pigmentation extended to the upper prickle layers, where the pigment appeared to be partly

intra-cellular. In the cutis, the pigment was found only inside the cells, not only in the perithelia of the blood vessels, but some distance away, especially abundant in the cells of the papillæ, which, in places, were all of them pigmented. The colour was here yellowish brown, the form that of well-margined granules; but the protoplasm of the cells was now and again diffusely yellow. In the neighbourhood of the papillæ, the cells were often arranged in rows, with their pointed processes directed to the epidermis, as if they were tending in that direction. Deeper down in the skin, the number of pigmented cells was much less. The density of the pigmentation of the cutis, and even of the papillæ, was not proportional to that of the epidermis. Nevertheless v. Kahlden regards it as so certain that the cutaneous cells have given up their pigment to the epidermic cells, that he concludes from the always considerable amount of pigment granules in the prickle layer, that several cutaneous cells have given up their pigment to one single epithelial cell. The blacker colour of the epithelial pigment is, according to him, only the result of the closer arrangement of the granules. The prickle layer of the hair follicles was pigmented in the same way as the surface epithelium, but only in their upper and middle parts; independently of this, some of the hairs of the papillæ were so deeply pigmented, that, even in the hair follicle, they looked like black rods.

v. Kahlden does not deny the relation of the pigmented cells to the vessels, he even found some pigmented cells in the intima; but such a constant and exclusively perivascular arrangement as Riehl and Nothnagel recognised, he could not determine, nor did he find, like the former, characteristic changes in the walls, thrombosis, or hæmorrhage. v. Kahlden had also, in his case, the opportunity of examining the black spots on the tongue, and found that most of the pigment lay in the papillary body, while the epithelium was very slightly or not at all coloured. Here also there were neither changes in the walls of the vessels, thrombosis nor hæmorrhage. But now and again free, amorphous pigment was present in the mucous membrane, and sometimes also in the engorged vessels, in the form of single, regular, black granules, usually free, but twice inside a cell (a white blood corpuscle ?), an observation on which v. Kahlden rightly lays much weight.

In a second, much less darkly pigmented case, he found the same conditions, only in slighter degree. Here there was in the deeper layers, free black pigment, in the form of amorphous granules and fragments; but there were neither changes in the vessels, nor hæmorrhage.

This work is by far the most thorough, and, histologically, the most accurate which we possess on the acquired pigmentations of the skin, and yet we can only with reserve, subscribe to the conclusions of the

author, "both general pathological grounds, and the position of the pigmented wandering cells in relation to the vessels, make the origin of the pigment from the blood probable," for in the first, very suitable case, neither was the iron reaction used to control the positive statements of Perls, which, in regard to the derivation from hæmoglobin, is more important than the position of pigment cells, nor is there any proof that the pigmented cells really wandered from the cutis, and could be recognised in transition form, at the border of the prickle layer, and inside it. Ehrmann's theory of pigment emigration without cell emigration, the assumption of the migration of an uncoloured matrix, and the independent formation of pigment in the epithelium and in the cutis, would equally agree with the appearances described by v. Kahlden.

Arsenical pigmentation.

This occurs mainly in two forms, firstly, in otherwise healthy skin after the persistent use of arsenic, and secondly, in other dermatoses (eczema, psoriasis) which, when healed under the influence of arsenic, leave behind unusually deep pigmentation. In the latter case the pigmentation has the form of the preceding disease; in the former it is diffuse, dirty greyish brown, and irregularly distributed. It affects also the palms, the soles and the nails.

Wyss found in a case of arsenical pigmentation in a choreic child, the pigment less in the papillary body than in the lymph spaces of the cutis. The basal prickle layer was very deeply pigmented. He assumed a destruction of the erythrocytes by the drug.

Manssurow saw a brownish discolouration of the nails, which appeared to depend on an orange yellow discolouration of the border of the nail cells.

Macula cærulca.

Since the works of Mourson and Duguet, we know that the maculæ cæruleæ of the older authors were caused by pediculi. They are greyish blue or dark blue spots, about the size of a lentil, appear in groups at the haunts of the pediculus pubis, the genital regions, the legs, and the axillæ, and usually soon disappear. Duguet was able artificially to produce the blue spots by the inoculation of the juices of the animal, and his pupil Mallet was able to show that it was chiefly associated with the salivary glands in the centre of its body.

Damaschino, who microscopically examined the spots under Duguet's directions, could find no cause for the colour, either in the cutis or in the epidermis.

($\gamma\gamma$). *Reflex Melanoses.*

Chloasma.

On account of the indefiniteness of the word chloasma, as used in literature, it is hardly possible to sum up the scattered short statements on the behaviour of the pigment in these cases. Here especially

are new investigations to be desired, with exact statements as to the cutaneous region examined, and the other pigmentary conditions. I have only once had the opportunity of examining a Chloasma of the face, of unknown origin, from a corpse, and found a purely melanotic pigment, as in ephelis, almost completely filling the under layers of the prickle layer, but in contrast to that, it was in an almost continuous layer, as high as the papillæ. In the cutis there was no pigment, neither free nor enclosed in cells. But the sub-papillary net was hyperplastic, and the papillary body very rich in spindle cells, and especially, like the rest of the skin, in mast cells. But I lay no value on this single observation, especially as the origin of the Chloasma was unknown.

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Section XV.

REGRESSIVE DISTURBANCES OF NUTRITION.

A.—With Degeneration Predominating.

1. With or without increase in volume.

Senile Degeneration.

We owe to Neumann the first account of the changes which senility induces in the skin. He distinguishes, in the connective tissue, three degenerative processes, of which the first two, the "coarse granular" and the "fine granular" clouding may pass into each other, so that the finely granular is a more advanced stage of degeneration, while the "vitreous swelling" represents a third, and mainly regressive metamorphosis. In addition to these degenerations, Neumann notes, fourthly, a general atrophy of the connective tissue of the skin, which he calls *senile shrinking*, and which he ascribes to a diminution of the papillæ in all their dimensions. The "fine granular clouding" gives the cutis a milky, the coarse granular, a greenish or yellowish colour; in the former, the fibres are almost completely replaced by granules, not staining with carmin, and insoluble in alcohol and ether; in the latter, they are mostly well preserved, and the coarse granules, which lie in rows between them and do not swell up but rather shrink with acetic acid, are due to the degeneration ("shrinking") of individual fibres. The two forms are frequently combined, the coarse granular predominating in the upper, and the fine granular in the lower part of the cutis; both may be present in layers or islands in the cutis. In the vitreous swelling, the fibrous bundles are replaced by a homogeneous mass, resembling gelatine. Nerves, vessels and epithelial appendages appear to be completely atrophied. The cutis is very much thinned, and brittle. Neumann identifies vitreous swelling with Weber's hyaloid degeneration, and, like this author, ascribes it to a primary change in the arteries.

These four changes Neumann found in all individuals over fifty, especially in the skin of the face, and this, according to him, was partly due to the external influence of temperature, and partly to the

continuous mimic movements of this region. It is also met with, well marked, on the neck of old women, and is possibly related to the swelling of the neck during pregnancy. In addition to these degenerations, there are often cellular infiltrations in the cutis, which Neumann regards as due to past inflammatory processes, distinguishing them from the senile changes.

Accumulations of pigment are almost always, though irregularly, distributed in the epidermis (especially in the scrotum) and the cutis (especially on the leg), and, according to Neumann, are the results of byegone disturbances of circulation. The smooth muscles of the senile skin indicate their regressive metamorphosis, by numerous "finely granular deposits," and shrinking of the rod-shaped nuclei. The epidermis is, in general, thinned, but the horny layer is here and there thickened, warty, and permeated by yellowish brown, or black pigment. The blood vessels he found invariably dilated, except in colloid degeneration of the skin, where they were narrowed or obliterated. The senile loss of hair can therefore not be ascribed to an atrophy of the capillaries of the hair papilla; it is a manifestation of the general involution of the cutis. Neumann found, in bald persons, complete hair follicles without hairs, but at the base, there were darkly pigmented clumps of cells, inside of which no papilla was recognisable. In advanced senile involution, we meet with cystically dilated or shortened follicles, filled with horny cells and fat; the dilated sebaceous glands open into these, and they therefore contain only smegma. The collagenous tissue of the follicle, as a rule, resists the senile changes longer than the surrounding cutis, and its fibres may be followed into the superficial fibrillary bundles, which still swell up when treated with acetic acid. In very old bald persons, we only find follicles shortened to their upper third, or others which have lost their epithelial contents, and only consist of a shrunken remnant. Rather remarkably, Neumann calls the depressions of the surface found at these places, which are naturally punctiform, "rugæ," and considers them as senile furrows. The coil glands are not atrophic, but are often filled with yellowish or brownish masses, by which the ducts may be dilated; these latter are often markedly oblique. In the fatty tissue, there is sometimes atrophy, with thickening of the connective tissue septa, sometimes increase of the fat, but there is no general rule. In experiments which Neumann carried out, to test the well-known experiments of Langer, with the skin of old people, he found both the extensibility and the power of retraction less than in younger skin, and he attributes the loss of elasticity to this degeneration of the collagenous tissue. Neumann says nothing of the elastin of the skin.

I have given Neumann's views thus fully, for it is the best work on the subject, and for twenty years remained the only one. Only recently M. B. Schmidt, using new specific methods for staining elastic tissue, has recognised that many of the structures described by Neumann are degeneration products of elastic tissue. Since these changes of old age are found especially in the skin of the face, which is notoriously rich in elastin, especially in the upper part of the cutis, where Neumann places his "coarse granular swelling," this change in our views on the degeneration was to be expected. According to Schmidt, the "fine granular clouding" and the "vitreous swelling" are also due to changes, partly mechanical, partly chemical, which occur in the elastin, so that the elastin degeneration is the main element in senile change of the skin, from the formation of the first elastin fragmentation to the transformation of the cutis into a structureless mass, *i.e.*, "vitreous swelling" of Neumann. Schmidt does not refer to collagen or to any senile degeneration of it. But its atrophy at the commencement leads to the approximation of the elastic fibres. As to the vessels, which Neumann regards as the point of origin of his hyaloid degeneration, Schmidt denies them any share in the regular senile involution, and regards the occasional limited changes in them (thickening, hyaline degeneration of the adventitia) as accidental complications. This radical upsetting of the views on senile involution is based on the following considerations.

The skin of the face from persons over fifty shows, with an elastin stain, that the power of taking that stain is, in general, somewhat diminished, though the sharpness of the specific colour is not influenced. The first change we see regularly in the well-known superficial elastic convolution of the skin of the face, the fibres being closer together and more winding. A broad, upper zone of the cutis, up to the invariably free sub-epithelial marginal streak, may consist of elastin alone, *without any collagen*, and hardly any cells. Schmidt thinks he can exclude a new formation of elastin, for there is usually a diminution in volume in the skin, and the papillary body is completely flattened. Neither excludes an increase in elastin; and whoever is familiar with the extraordinary abundance of elastin on corresponding parts of the skin of younger persons, will be able to explain the appearances, without the unlikely assumption of an elastic new formation. On this there follows a further change of the elastic fibres, in one of two directions: either hyalin swelling, or granular degeneration. In hyalin swelling, there develope thick, shining, homogeneous, sometimes elongated bands, with knotty thickenings, so that the fibres sometimes appear like strings of beads. But they still stain like normal elastin, and with an eosin-hæmatoxylin stain, unlike free hyaline substance, they take, not

the eosin but the hæmatoxylin. In addition to the swollen fibres, we find hyaline fragments, which are partly due to swelling and subsequent breaking down, and partly to the unrolling of swollen fibres. In the latter case, we sometimes find compressed cells enclosed in them. In the breaking down into angular or rounded granules, the form of the fibres is still recognisable by the serial arrangement of the granules, or they may run together into collections of spheres, which largely contribute to the "granular" appearance of the sections. According to Schmidt, the "granular clouding" of Neumann depends on two factors; the coiling-up, and the breaking-down of the threads. While the hyaline degeneration appears primarily in the fibres which are not breaking down, it is, according to Schmidt, added secondarily to those which are broken down into granules, and forms, when they run together, still larger vitreous areas. The transition of the fragments and granules, *i.e.*, the broken down fibres, into a homogeneous mass, is proved by the fact, that there are fragments which are partly granular, partly homogeneous, and that in convolutions which are completely transformed into granular masses, homogeneous spots appear. "These appearances lead, continuously, to a stage, in which, at first, the convolution of the upper cutaneous layer, and finally its whole thickness, is occupied by a completely structureless, homogeneous mass."

While Neumann determined a four-fold change, Schmidt gives us an apparently uniform view of the senile involution of the skin. Whether this is attained without doing violence to fact, is somewhat doubtful. For Schmidt draws his exact description from the upper part of the cutis, and the application of this to the whole skin of the face is, to anyone acquainted with the latter, not sufficiently justified by the words just quoted, for, deep down in this region, there is no widespread elastic convolution, which makes Schmidt's theory so plausible for the upper cutaneous layers.

Reizenstein has very briefly investigated Schmidt's results, and has in general confirmed them. He ascribes the orcein stained mass in the papillary body of the cheeks (which Schmidt ascribes to the swelling) to the later breaking down into granules, and the ultimate confluence of the swollen fibres and granular products of degeneration into homogeneous, hyalin masses, but does not find the latter in the deeper layers of the skin. There, according to him, there are only the changes familiar in elastic fibres, button or bead-like swellings, breaking down into collections of granules, splitting, fissuring, and widening, with loss of staining power. An important difference in the statements of Reizenstein, compared with those of Schmidt, is, that the former found exactly the same changes in the elastic tissue in young people of twenty-six and twenty-eight, so that either the commencement of

senility is much earlier than we had previously assumed, or other processes than senility may lead to the changes.

I too have tested the statements of Schmidt on the facial skin of four young and eight elderly people. The elastin was demonstrated by means of acid orcein. This is found, assuming the condition in younger people to be normal, increased, in older people, in the papillary body and the upper layer of the cutis, and I also believe that this increase is not due to new formation, but is the simple result of an irregular thickening of the fibres. They form, directly under the sub-epithelial margin, a close felt-work of fibres and clumps, which often reaches to the under margin of the upper third of the cutis. But I cannot admit that the cutis here consists only of that felt of elastin. Even a simple after-stain with polychromic methyl-blue suffices to show that, at the densest areas, a net of collagenous fibres is enclosed. No doubt here the collagen also frequently undergoes a regressive change, which perhaps makes its recognition a little more difficult. It stains less easily with acid and neutral colours, but readily takes up basic ones. If the sections are stained with polychromic methyl-blue, and decolourised in neutral orcein, all the collagen takes a dark orcein red colour, and only the degenerated parts remain blue. We can now readily see that these "blue" areas in the skin of the face of elderly people, especially in the upper parts of the cutis, are seated in the neighbourhood of elastic convolutions, but *usually somewhat deeper*, and reaching further inwards; that in place of circumscribed areas, in some cases, widespread nets of "blue," *i.e.*, basophilic collagen run through the cutis; and that, in comparing serial sections, stained, some for collagen, some for elastin, the degeneration areas of the two substances do not exactly correspond, but lie hard by one another or run through each other, as is very clearly seen with the double stain mentioned above. That this is really a change in the reaction of the collagen is seen by the reverse stain with water-blue and saffranin, in which all the collagen takes the acid water-blue, with the exception of the basophilic areas, which stand out saffranin red, on a blue ground.

There consequently exists in senile skin, along with the elastin change, a considerable collagenous change, especially in the upper layers of the cutis. This relates not only to the reaction of the collagen, but also to the form of the fibres, which—just like the elastic ones—swell up, round off, and break down into varied sized fragments and granules. We often find, enclosed by a dense elastin net, a loose collection of granules, and fragments of basophilic collagen, and I am convinced that Neumann, in Fig. 56 of his text-book, had before him, in the round area of "degenerated cutis," not elastin but fragments of collagen, while, on the other hand, the "granular clouding" in Fig. 53 consists, from its position and form, of elastin fragments.

With the double stains just mentioned (methyl-blue, neutral orcein; water-blue, saffranin), I found invariably, in the central and lower cutis, large, winding, broad fissures and bundles, taking the methyl-blue or the saffranin, which are remarkably like ordinary thick elastic fibres. But in these sections no single elastic fibre is stained, a staining of elastin in basic solution of basic colours is unknown. But if one compares those sections with subsequent ones, stained with acid orcein, we note that these fibres and fibrous processes are of the nature of elastic tissue. Only the fibres which have taken the (red or blue) basic stain correspond to those which take the elastin stain *very faintly.* Diminution of staining power in the elastic fibres has been noted by Schmidt and Reizenstein; but they have not noticed that we have here a completely altered elastin, a basophilic substance. The fibres are usually less bent, often swollen, and, with the simultaneous diminution of their staining power, may have been regarded as swollen and breaking down elastic fibres. But that, they are not; they are rather very persistent, and we will find them in very chronic affections, in scars and in colloid degeneration of the skin. For these reasons, a special name is necessary for this substance, and, in view of its tinctorial properties, and to recall its origin, I call it *Elacin.* In addition to the stains mentioned, elacin is very well demonstrated in sections stained with polychromic methylin-blue, by decolorising with tannin, or a mixture of acid fuchsin and tannin. In the latter, very beautiful demonstration of elacin, some bodies in the upper cutaneous layers take the same deep blue colour as the elacin. They are found inside the first-mentioned degenerated areas of the collagen, and look like angular or rounded fragments of some substance lying over the areas. Some of them represent portions of thick, split-up trabeculæ, others, round fragments, and others, rounded winding fibres and fibrils, or angular granules of the most varied forms. The smallest ones will, on account of their deep blue colour, be regarded at the first glance as nuclear fragments. But the larger ones show by their form a connection with collagenous or elastic fibres. They can certainly not be simply elastic fibres, which have altered their staining power like elacin. If we compare such places with corresponding ones in orcein and methyl-blue-tannin preparations, we see that there is so far a connection with elastin, that there are fragments of collagenous trabeculæ, which are covered and permeated by basophilic elastin granules, *i.e.*, elacin granules, and thus have assumed the staining power of elacin. It is consequently a replacement of the collagen by elacin, and thus there developes a substance which combines the form of collagen with the staining power of elacin, and to which I will give the name *Collacin*, since we will meet it in greater extent in the

process of colloid degeneration, and there it must be clearly distinguished from elacin on the one hand, and colloid on the other.

Like the elacin, elastin may also combine itself with degenerated colloid. But the combination of the two substances is not so readily recognisable as the collacin, for the product which developes has the stain of elastin, and therefore must be distinguished from true elastin, mainly by its form. It is certainly often possible, with careful counter-staining of elastin preparations, to recognise, in fragments of apparently pure elastin, a collagenous nucleus, especially if it show basophilic reaction. In this way I would explain the peculiar large structures figured by Reizenstein (Fig. 2), which take, inside, the methyl-blue, and at the periphery, the orcein stain, and which, in their form, resemble collagen much more than elastin.*

I would not have been so definite regarding the substitution of collagen by elastin and elacin, were not these changes most typically present in colloid degeneration of the cutis, and in Myxœdema.

I suspect that Schmidt overlooked the presence of collagenous tissue and its degenerations, because he did not attempt to distinguish the elastin-stained collagen from the rest of the elastin. And I see no reason to speak of a hyaline degeneration of the breaking down elastin; these appearances are, in my opinion, due either to swelling and fragmentation of the collagen, with the adoption of basophilism, or to combinations of elacin and elastin with collagen. Then I cannot admit that, in simple senile skin, the outer third passes into a substance resembling elastin. The central and under layers of the cutis consist, in all my preparations, partly, as usual, of collagen and elastin, partly of reticular basophilic collagen and fibres of elacin.

It is only of historic interest to compare the results got with modern methods, with Neumann's old category of the degenerations. From his description and drawings, the fragmentation and coarse felting of the papillary elastin is the basis of his "coarse granular clouding." His "fine granular clouding" may correspond to one of several things; the breaking down of the collagen, or granules of elacin and collacin. More important is the question of the existence of the complete vitreous swelling, which he regards as the highest degree of senile change. The works which I have named no more point to it than do my own preparations, and one might doubt its existence, did not Neumann's drawings clearly demonstrate an extremely severe and rare degeneration. Here is a want whose supply is very desirable; is this a true hyalin (acidophilic) formation, or a swollen basophilic collagen, a degeneration of collagen or elastin, or of both together?

* I call this combination of collagen with elastin, *Collastin*. This substance we will meet again in colloid degeneration and in Myxœdema.

So far as concerns the other changes mentioned by Neumann, I can confirm most of his statements: the increased pigmentation and the general atrophy of the epidermis, the shortening of the hair follicles and the dilatation of the sebaceous glands, the integrity of the sub-epithelial connective tissue streak around the follicle, which does not undergo degeneration, the dilatation, or gaping of most of the capillaries, which is due to a greater stiffness of the connective tissue, and, in places, to a slight thickening of the walls, and the occurrence of scattered cellular areas. As to the latter, I do not regard them as accidental residua of byegone inflammations, for I have met them in all old skins where degenerations of the cutis were going on, and I therefore regard them as a manifestation of senile involution. The cell bodies are small, mostly spherical; the nuclei relatively large, some indeed very large, and deeply stained. There were no plasma cells, and mast cells were present in normal numbers. Unlike Neumann, I found no degeneration of the muscles. On the contrary, they were usually numerous on the face and scalp, well stained, and surrounded by relatively well formed elastic sheaths. But I often found sections in which an oblique arrector ended in an area of collagenous and elastic degeneration, so that it had lost its point of attachment. It is not impossible that the localisation of senile changes to circumscribed parts of the papillary body has some connection with the attachment of the muscles at these places. Otherwise the topography of the change, which is marked on the exposed areas, points to the fact, that these degenerations are not simply a senile change, but are rather due to years of exposure and to external injury, especially to the action of the weather on the ageing skin. I regard only general atrophy of the skin as a pure senile change.

In alluding, in conclusion, to the question put by Reizenstein, I must first remark, that the appearances of degeneration were different in each one of the cases I examined, that the combinations were different, and that they were not proportional to the age. A specimen from a patient aged 49, showed more change than one from another aged 67. If we regard this senility of the skin as due to the weather, this incongruity may be explained. But then the limit of senility will be difficult to draw. The material which I have examined in this connection came from cases 1, 5, 21, 25, 44, 45, 49, 65, 67, 76, 78, and 80 years of age, and in addition to the skin of the face, I have twice examined that of the hairy scalp and the neck. Now I found that, in general with advancing age, the clumping and felting of the papillary elastic convolutions increased, and that we met with delicate elastic processes only in younger persons. But I must agree with Reizenstein, that evidence of these changes is present, even before the

fortieth year. But since I do not regard simple swelling and breaking down of elastin as the main and ultimate characteristic of senility, but rather the degeneration of collagen, and the combination of the degeneration products of both into a uniformly staining substance, I cannot allow to his question the position which it would possess, if the changes in the elastin were the measure of senility.

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Cutis hyperelastica.

By cutis hyperelastica, I understand the skin of the so-called india-rubber men, who are able to draw out their thin, soft skin, in different parts of the body, in all directions, sometimes as much as a foot. When released, it returns to its original condition with an audible snap. This affection has been comparatively often described under the not very appropriate name of "Dermatolysis" or "Cutis laxa," but has only recently been histologically investigated. The favourite name, Cutis laxa, is not particularly appropriate to the main histological phenomenon, the retained elasticity of the skin, and would rather apply to a sort of spontaneous formation of inelastic folds, such as are found in certain cases of Elephantiasis congenita, Pachydermatocele, in Myxœdema and senile skin.

Kopp, who observed the affection in a father and son, believed that the abnormality perhaps depended on an acquired increase of elastic fibres, but mainly on a congenital and perhaps atavistic defect of that connective tissue which usually unites the cutis with the underlying tissue, fascia and periosteum, and at certain places is especially well developed. The stretching would of course favour its development. He made no histological investigations.

Du Mesnil, by a comparison with folds of normal skin, showed that, with the abnormal formation of folds, it could not be simply an excessive mobility, but that the skin was abnormally extensile. The retinacula of the skin must also be of excessive extensility, and perfectly elastic,* because the skin rapidly and completely returns to its old position. On comparing the piece of skin from the breast of a man of nineteen with Cutis hyperelastica, with a piece from a normal breast, Du Mesnil found no distinct difference in the number of elastic fibres,

* We should avoid the use of the terms "great" or "high" elasticity (which often occurs in the works in question), if we wish to say that the skin may be greatly extended and immediately return to its original position. The physicist, certainly against the popular expression, calls that *slight* elasticity, since extension may take place with slight force.

but they were more twisted, and the elastic net narrower and more irregular. The epidermis was drawn into folds, which fact Du Mesnil ascribed to the great contraction of the piece of skin, by hardening in alcohol. The cutis, when fresh, had the feeling of colloid tissue, and consisted, microscopically, of a structureless homogeneous mass, which was permeated by stellate and spindle cells, and elastic fibres, from the epidermis to the panniculus. Only the enclosed follicles, coils and vessels were surrounded by thin layers of spindle-celled, ordinary connective tissue, which here and there contained areas of round cells or leucocytes. Du Mesnil regarded the myxomatous nature of the cutaneous connective tissue as an arrest of development, as the persistence of the cutis in an immature, embryonic condition, like that of the umbilical cord. Even the scar of the excision wound, which was stitched, and which, after eight days, instead of a linear scar, was $1\frac{1}{2}$ centimetres broad, appeared to have assumed this myxomatous character, and, itself inelastic, was stretched by the elastic strain in the neighbourhood, as all the scars in the patient were.

I had the opportunity of removing a piece of skin from this patient, which Williams examined in my laboratory. He, too, could, only with great difficulty, recognise a slight alteration in the elastic tissue, a more wavy course of the fibres, shown by their shorter sections and more numerous cross sections; the fibres in the papillary body were finer than normal. The number of the elastic fibres was not increased, but their length was, probably as a result of the constant stretching. Greater changes were seen in the collagenous tissue, in that, in the deeper layers, the broad bundles were absent, but many more numerous smaller and longer ones were present in their place. Otherwise, Williams found the fibrillary structure of the collagen normal; the splitting-up which he described in the uppermost layers is also normal, though perhaps not usually so marked as here; but it is a slight abnormality, that the fine fibrillæ and the cells of the papillary body are embedded in a homogeneous mass, which does not take the water blue so well as the fibres of the deeper cutaneous layers. The connective tissue cells were normal, and no mitoses were evident. Williams thought the muscles somewhat more numerous; mast cells were present in abundance. Both the larger vessels and the fine capillaries showed an abnormally winding course, and thus several cross sections of the same vessel were seen close together. The blood capillaries, lymph vessels and lymph spaces were dilated, and the blood vessels often surrounded by leucocytes. The longer and winding course of the nerves corresponded to that of the blood vessels. The epidermis was—as in Du Mesnil's preparations—very much folded. But Williams found, on comparing his preparations

with those from the normal lumbar skin, that the surface epithelia were larger, and the sebaceous glands more voluminous than normal. On digestion with pepsin and trypsin, the protoplasmic elements of the cutis were more rapidly digested than usual, while there was no apparent difference in regard to the collagenous substance.

Like Du Mesnil, Williams found the main cause of the extensibility of the skin, in a special yielding. There comes into consideration, in a minor degree, the insufficient adhesion to the tissues beneath, which is shown in the altered structure of the collagenous septa of the fatty tissue. According to him, the extensibility of the cutaneous tissue finds its microscopical expression in the bending, twisting, and spiral winding of all the constituents of the skin, and the perfect elasticity, in the comparatively slight changes of the elastic tissue. The striking incongruity, in regard to the structure of the collagenous tissue, between his examination and Du Mesnil's, Williams refers to the more advanced degeneration of the skin of the breast, which Du Mesnil examined. He regards the slight degree of homogeneity of the papillary body in his case, as a commencement of the myxomatous change, which in Du Mesnil's specimen had gone on to total degeneration of the cutis. Against a congenital interference with the formation of collagen, was the fact that the elastic substance was fully developed, and that the whole affection developed first at the period of puberty, and quite irregularly in different regions.

I have, at different times and with different methods, examined the same material as Williams, in the hope of finding a more satisfactory solution of this rare cutaneous alteration, but without success. Even were the spiral twisting of the vessels and nerves, and the greater bending of the elastic, and greater separation of the collagenous fibres, sufficient foundation for the extraordinary extensibility of the skin, the still more remarkable symptom of increased power of retraction of the stretched skin, with no alteration in the elastin, is not so easily understood, and less so if, as I believe, a certain, though limited part of the elastic fibres are converted into elacin. Possibly, this true degeneration is to be regarded as an effect of the daily over-stretching * of his skin. In general I can confirm almost all the statements of Williams, and like him I lay most weight on the windings of the vessels and nerves, which are capable of such extension. For these are the structures whose connective tissue surroundings form the retinacula of the skin. It must be noted, that all the enclosed organs in the skin are much more freely movable than usual; most of the innumerable fine connective tissue fibres, by which they are normally united with the cutaneous

* The man was in a travelling show (Dime Museum).—N. W.

fibres, are absent; either they have been torn through or have never been present. Therefore there exist, at the borders of all these organs, follicles, coils, vessels, nerves and muscles, distinct, but not wide lymph spaces, and thus perhaps the appearance of œdema. But there is no true œdema, and this is a point in which I differ from Williams, who describes a slight œdema. I will further note, that I could not find the slightest *inflammatory* cellular infiltration around the vessels, and no leucocytes. The vessel walls are simply more cellular than normal, which is explained by the fact, that during life they were often over-stretched, and are here retracted. Thus the attempt to explain the myxomatous condition of Du Mesnil's preparation fails. In general, I find the mucoid condition of the papillary body not very distinct; it consists in a somewhat greater spread of the connective tissue fibres, which usually are sharply stained by water-blue and neutral orcein, and, with a double stain with the two colours, form a very dense felt. Inside them no mucin takes up methyl-red. Further, I was not able to recognise in the collagen, especially of the upper layers, any sort of degeneration, which would correspond to the partial transformation of elastin into elacin; I found neither collastin nor collacin.

So I am, like Williams, compelled, by exclusion, to assume that, in our case, the great extensibility of the skin depended on the winding and narrowing of the vessels, nerves and elastic fibres, and on the splitting of the collagenous substance. This latter appears to me to be very important; it is extreme. With a water-blue-neutral orcein stain, which shows the contours of all the fibrillæ, we have, from the papillary body down to the hypoderm, a regular mass of short, winding collagenous flakes, without any connection by coarse and long trabeculæ. It would therefore be interesting, in future investigation, to observe the lines of tension, which cannot be of their normal sharpness.

It appears to me that the exquisite contractility is not sufficiently explained by reference to the preservation of the elastic fibres, even apart from their partial degeneration. But I am unable to throw any light on this most important point. It may be that further investigations will show that the cutaneous muscles are always increased. Williams hinted at such a hyperplasia; I also found, in many sections, unusually numerous, oblique cutaneous muscles. This point deserves thorough investigation, for a hyperplasia of the muscles would naturally and simply explain the perfect elasticity, and the great contractility of the skin. If this be the case, we shall have to remove the affection from the regressive changes, under which, resting on Du Mesnil's observations, I have placed it, and place it in the class of progressive disturbances of nutrition.

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Colloid Degeneration.

(Miliary colloid, Besnier ; Hyaloma, Vidal-Leloir.)

This affection has as yet only been found in elderly persons, who have been long exposed to the weather. It appears in the form of small, irregular, shining, yellowish, transparent, hard spots, which occupy the upper part of the face, the neck, and the backs of the hands, are partly *in* the skin and partly project over it. Although they often occur in groups, they never run together. On squeezing the nodules, a transparent gelatinous mass is discharged.

They were first described by E. Wagner, under the name *Colloid milium*, and then by Besnier under the correct name : *colloid degeneration of the skin ;* Liveing has published three cases, without histological investigation.

Balzer, who investigated Besnier's case histologically, found, on examination of the expressed contents of the nodules, that the colloid mass depended on a change of the collagenous fibres, while the enclosed connective tissue cells and glands were intact. At the top of the nodule, the epidermis is thinned, and the papillary body flattened, but everywhere preserved, in the form of a fine band between the colloid mass of the cutis and the epidermis. The nodules only press the healthy follicles and glands aside, and are separated from them by a fine zone of healthy connective tissue. The colloid infiltration of the cutis is seen mainly in the sub-papillary region, first as a simple alteration of staining reaction, the collagenous bundles staining not rosy red but a dark orange, with picro-carmin. Further outwards, only a few fibrous bundles show this reaction. As degeneration advances, they swell up and run together into large, shining blocks. The nerves remain normal, but the blood vessels show a colloid, not amyloid degeneration of their outer sheaths. This is not limited to the neighbourhood of the colloid blocks, but sometimes the vessels are surrounded by bundles of degenerated fibres. Collections of cells around them are found especially where the degeneration is not excessive ; they do not alter the purely regressive character of the affection. Balzer is inclined to place the point of origin of the colloid affection, in the sheaths of the vessels.

This careful investigation established even in Wagner's case, that

this colloid, coiled mass was not an epithelial formation (Milium), as Wagner thought, but a degeneration product of the cutis.

Ten years later, Balzer had again the opportunity of examining, microscopically, a similar case of Feulard's. In this case, the disposition of the colloid blocks in the upper part of the skin, between the follicles, was the same, but the colloid degeneration was also evident in the hypoderm, and the sheaths of the follicles were partly degenerated. In contrast to the first case, Balzer found some collections of cells between the plugs, partly colloid, and in this case he does not derive the affection from the vessel walls, for the vessels were all permeable, and the affection was clearly seated in the most a-vascular parts of the cutis. Around the colloid blocks, Balzer found well-preserved elastic tissue. At the seat of the degeneration, the elastic fibres were thinned, and broken down into fragments, or no longer stained. Balzer finally defines the affection as a colloid infiltration of the connective tissue bundles, which swell up into compact voluminous masses, compress the other constituents of the skin, and form cavities in the cutis, from which the colloid masses are readily shelled out.

Perrin has recently published a case of this rare condition, which was examined microscopically by Reboul. He confirmed, almost verbatim, Balzer's facts; his only novelty is a colloid degeneration of the perineurium, without any other changes of the nerves. He lays more weight than Balzer on the colloid vascular changes, and the cellular infiltration which occurs in the centre of the colloid zone. Reboul does not mention the changes which Balzer describes in the elastic tissue.

By the great kindness of Dr Perrin, I received a piece of a nodule from this last case, and its examination enables me to add certain details to the descriptions of Balzer and Reboul. It is evident that the application of the specific stains for colloid and elastin, which are mentioned in different parts of this book, are absolutely essential for studying this affection, and it was likely that the facts mentioned concerning elastin and collacin, in connection with senile skin on the face, would be of great value in the explanation of the colloid masses which are found in this affection, for it only developes on the basis of senile facial skin. I found that the fainter stain of the elastic fibres, which Balzer described, was only limited to certain areas underneath the colloid blocks, and was due to a transformation of elastin into elacin. With a basic stain with methyl-blue or saffranin, the fibres appear all the more definitely. The colloid blocks are then, as Balzer rightly states, surrounded by a shell of elastic tissue, which retains only a shadow of its form, and is mostly broken down into drops, fragments and smaller granules; just as in every senile skin of

the face. But Balzer naturally could not suspect that, even in the colloid blocks, a considerable quantity of elastin persists. The smaller blocks at the border of the nodule give, with acid orcein, sometimes completely, sometimes in segments, the dark brown reaction of elastin, an appearance which at the first glance appears to favour the view of Schmidt, that the colloid substance of senile skin is only altered elastin. But on careful examination it is seen that the matter is by no means so simple.*

A pure collagenous stain shows that, from the normal collagen on the surface, and in the deeper parts, there is a regular progression up to the colloid blocks; at first the fibrous bundles stain more faintly, and show only a few deeply-stained fibrillæ, then they split up into fine fibres, and finally into granules, of the most varied form. This loose structure of granules condenses into a more compact mass, of granular structure, which becomes homogeneous, first inside, then at the borders, and ultimately represents a section of a large colloid block. An acid orcein stain also shows a gradual transition from the few remains of well-preserved elastin, up to the colloid blocks. The elastic fibres first break down, exactly as in senile skin, into drops or a series of tubes, coarse pieces or fine fibrils, and form altogether a loose fibrous felt, which contains everywhere a few thicker elastic fragments. This felt-work is ever condensing, and finally forms a large clump, which is homogeneous from the centre to the border, and then also represents a segment of a large colloid block. There is only this difference, that the degenerating elastin always retains its specific stain, while the degenerating collagen, from the commencement, stains less.

A good double stain (*e.g.*, water-blue orcein) for collagen and elastin, shows that only at the commencement are the two changes distinct from one another, and they soon become mingled, in that the degenerating products combine into a new body; Collastin.† Where, with elastin stain, the dense brown felt, and with the collagen stain, the dense granular mass appears, the combination is almost complete. The *colloid* is developed from the collastin by homogenisation and swelling; with its appearance the elastin stain is lost. The surroundings of the nodule in the upper two-thirds of the cutis contain only a little collagen and elastin; they mainly consist of collastin, with the reaction of elastin.

So far, the process is relatively simple; but now we find that at the very commencement, a few elastic fibres (in the depths of the skin),

* I can only shortly refer to the complex conditions, which require a somewhat careful tinctorial technique, and will consider them more fully in another place.

† See chapter: Senile degeneration.

a few drops aud fragments of elastin (in the upper cutaneous layers), and finally, certain parts of the loose elastin felt-work are transformed into basophilic elacin (see page 981). This takes no part in the formation of the colloid, but represents a sort of appendix to the general degeneration process, the whole elacin fibre persisting as such, and the elacin drops and elacin granules combining with the collagen to form *collacin*. I have never before met with the formation of collacin in such extent and abundance as here. An isolated stain of it is got by the acid fuchsin-picrin method, since with this, elacin, elastin and colloid take no specific stain. On the almost completely yellow background, appear the fibres, fragments, blocks, and the coarse split trabeculæ of collacin, in dark almost black red colour, and we see that these are quite irregularly collected on different places, but, as a whole, are not very numerous in the colloid blocks and the surrounding collastin.

There are consequently, in this regressive metamorphosis, two allied processes, of which only one gives origin, by the enormous swelling of its products, collastin and colloid, to the macroscopically evident protuberances, while the products consisting of elacin and collacin, are only microscopically evident. The collastin and the colloid on the one hand, and the collacin on the other, have the peculiarity in common, that they develope from the collagenous substance, under the influence of the dissolving, changed and unchanged elastin.

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Myxœdema.

The clinical characters of this disease, described by Gull, Ord and Charcot, are so distinct and familiar, that a confusion of Myxœdema of the skin with other skin diseases, especially with ordinary œdema, can hardly occur. I therefore turn at once to the unfortunately very scanty results, which histological investigation of this most interesting affection has provided.

Ord, in examining bodies of patients dead of myxœdema, found, in the different organs and in the skin and hypoderm, a mucus-like substance. To this he attributed the peculiar sodden, elastic condition of the skin, which is only œdema-like to the eye and not to the finger, and he founded on it the name, Myxœdema.

Virchow, who had the opportunity of examining histological preparations of Myxœdema in London in 1886, stated, in a lecture in February 1887, that there was present in it, a growth of the connective tissue in the cutaneous and superficial portions of the skin, with such abundant nuclear and cellular division, that in many places the appearance was that of granulation tissue. It is not the fat cells themselves which grow, but the processes of interstitial connective tissue; the fatty tissue becomes atrophic. This observation of irritative, perhaps inflammatory changes in the skin was, for Virchow, all the more remarkable, since, from the description of English authors, he had regarded the affection as a purely passive stagnatory formation, with the accumulation of mucin, and eventually a metaplasia of the fatty tissue into mucous tissue. Of this latter degeneration nothing was visible, but the preparations which he examined were "not suitable for deciding in what way the mucin occurs in the tissue, and where it remains."

From this communication, we take the following: "the remarkable thing is, that these (irritative) changes are almost absent in the surface of the cutis, while the *deeper layers of the cutis* and the upper layers of the subcutaneous tissue are affected." But this localisation, which Virchow rightly regards as remarkable, does not appear to be present in all cases or stages, for in a later demonstration, of a London preparation from the eyelid, he says that, "*directly under the papillæ*, an excessive growth takes place, by which the whole part, which otherwise contains few cellular elements, appears to be filled by dense nuclear and cellular material."

Caspary had the opportunity of examining a piece of myxœdematous skin from the face, and found quite different appearances. In the epidermis, the glands and the muscles, he could recognise no changes. But there was seen in the upper layers of the cutis, an almost complete disappearance of the collagenous tissue, and a moderately striking prominence of the elastic tissue, numerous spaces filled with finely granular contents, with few cells and very few blood vessels. Further, Caspary noted peculiar, shining fragments, whose nature he could not explain, but which we now (see Senile degeneration of the skin) recognise, in every old facial skin, as degenerated elastin and collagen (the patient was 58). The hypertrophy of the elastic tissue is now known to be normal in the papillary body and the upper cutis of the facial skin. In the deeper layers of the corium, the connective tissue bundles were normal; Caspary could not determine irritative changes, either there or in the hypoderm.

Baumgarten got a piece of the skin of the neck from the same case, which had previously been very much thickened, and found only a striking development of the elastic fibres, and a marked accumulation

of leucocytes immediately around the cutaneous vessels. This was increased in places, to form sharply-marked leucocytic foci. Otherwise there were no deviations from the typical structure of the skin.

While, consequently, Caspary's observations on the facial skin of this case were almost negative, Baumgarten's observations are more like those of Virchow.

Then come some observations which more harmonise with the first ones of Ord. Campana found the fibrillary structure of the skin partly gone, and replaced by mucous substance. Schwass saw, on incising the skin of the thorax, a transformation of the hypoderm into a "gelatinous, thready mass." Ord, who spoke at the International Medical Congress in Berlin, stated that the connective tissue, not only in the skin but in all the organs, was increased, rich in nuclei, and filled with inflammatory products. In his first patient, who died when the disease was fully developed, a large amount of mucin was found in the tissues. "Later investigations have certainly not confirmed this, which is not remarkable, considering the differences in the cases, and the different conditions under which the patients died." At the same time, Mosler spoke of the tense elastic feeling, like stiffened gelatin, which the skin presented, and which was produced by the increased amount of mucin.

From these quotations it is plain, that different objects, and probably different stages have been examined, for an abundance of inflammatory cellular infiltration, on the one hand, and a complete absence of it, on the other, a complete transformation into gelatinous mucoid tissue here, and an absence of mucin there—such statements cannot be reconciled in any other way. At most, mucin might, in hardened preparations, have escaped detection, having been lost in the processes of preservation, but this is not likely, considering its insolubility in alcohol, chromic acid, and osmic acid. In this connection, modern staining methods for mucinous substances make things easier. It appears to be established, that the elastic tissue is increased and the collagen diminished (Baumgarten, Campana).

Future investigation has chiefly to be directed to the following points: the behaviour of the collagen and the elastin, and the presence and the spread of mucin and cellular infiltration. That cellular infiltration accompanying other changes is not proof of the inflammatory nature of the process, we see by its occurrence in simple senile skin.

By the kindness of Dr Norman Walker, I am able to contribute a little to the solution of this question. The piece of myxœdematous skin which he sent me, came from the scalp of a patient aged 56, who died from syncope while the condition was improving under thyroid gland.

There was, to take this point first, not a trace of cellular infiltration or leucocytosis, although in general all parts of the cutis, even the vessel walls, were somewhat more cellular than normal. All the cells were very poor in protoplasm, spindle-shaped, and the nuclei generally rod-shaped, as one usually finds them in the cutis, only where some form of pressure, *e.g.*, of hypertrophic collagenous tissue, has acted on the cells and nuclei. This form of the cells is the more striking, since, with nuclear and protoplasmic stains, the cutis, but especially the papillary body, appears to be everywhere beset with large spaces, and this incongruity indicates a substance present, or previously present in the tissue, which cannot be made visible.

Staining for collagen, elastin and elacin gave surprising results. In my preparations, the collagen is distinctly less. There is certainly no firm collagenous frame-work in the cutis, but only a loose arrangement of fibres, like basket-work. The acid fuchsin-picrin method determines how much of this is collagenous. We see that almost all the (red) collagenous fibres run, very loosely packed, parallel to the surface, and increase in thickness from above downwards. Between the fat lobules are found very thick collagenous bundles, which have the same loose arrangement and winding form as the finer fibres of the cutis. The very much thickened papillary body consists of very fine collagenous fibres, which run in all directions, with distinct, apparently empty spaces between them. Staining with acid orcein for elastin gives, in a certain sense, a similar appearance, in that there is not the normal permeation of the collagen, but the fibres are mixed with collagenous ones, and, like these, run horizontally, in wavy lines. But while the latter, on account of the numerous holes, appear to be diminished in number, the elastic fibres are distinctly multiplied, especially in the cutis proper, while the garland-formed net of the papillary body is normal.

So far, we have only determined an enclosure of the cutaneous fibres, and a not very important degree of deviation from the normal. But matters alter when we apply more delicate staining methods to the study of the qualitative changes. Decolourisation of methyl-blue sections with neutral orcein, shows that many of the collagenous fibres, and more, the more they are in the hypoderm, do not, like healthy collagenous fibres, greedily take up orcein, but completely or partially retain the basic methyl-blue. There consequently exists a distinct basophilism of the collagen. But the elastin is altered in the same direction, and to a greater amount. For, if one stains the collagen with water-blue, and counter-stains with carbolic fuchsin or saffranin, an astonishing number of fibres take the red stain, though they resemble the elastic fibres in all but colour reaction, and we must

regard them as *elacin* fibres or basophilic elastin fibres (see the chapter: Senile and Colloid degeneration). I have found these elacin fibres more numerous in this myxœdematous skin than anywhere else. We further note, that not only a greater proportion of the elastic fibres is transformed into elacin, but that the same colour reaction extends to the medium and thick collagenous bundles, which are clearly recognised as such, by their terminal breaking down into fibrillæ, and their longitudinal marking. There consequently exists the same replacement of collagenous fibres by elacin, with which we became acquainted in colloid degeneration, and to whose product we have given the name Collacin.

These simple stains are not sufficient to establish definitely these remarkable changes, for, as we saw, there is a widespread basophilism of the collagenous fibres, and we might attribute this stain to the fact, that the carbolic fuchsin stains, without distinction, basophilic, elastic, and collagenous fibres. Sections which are simply stained with methyl-blue and neutral orcein show, that the often-mentioned coarse trabeculæ of the hypoderm do not stain equally on cross sections, but show a blue mosaic, surrounded by brown lines, and still more deeply browned external, marginal lines. In some sections the brown septa divide gyrate blue areas; and here the bundles were consequently not composed of sharply-rounded fibres, but represented folded, adjacent plates. We also see, with the water-blue carbolic-fuchsin method, that the inside of many of the coarse fibres prefer the basic, and the outer surface and the septa in the interior, the acid colour. This would be very remarkable if these fibres consisted entirely of collagenous substance, but is more comprehensible if a deposition of elastin has taken place on the outer surface of the collagenous fibres. Only triple stains make this quite clear; we first stain all the elastic tissue with acid orcein, then the collagenous tissue with water-blue, and finally, with carbolic fuchsin, remove these stains from all basophilic degenerated parts. Here we find single, fuchsin-red, coarse bundles, covered with elastic, brown plates, and permeated by finer ones. Were, as is possible with the double stain, the difference in colour only due to the fact, that each bundle underwent basophilic degeneration from within outwards, and therefore showed an external non-basophilic layer, this, with the triple stain, would have been stained water-blue, and would not have taken the acid orcein stain, characteristic of elastin.

I have described this technical point so fully, because it is new and very important. It is certain that some of the basophilic collagenous fibres are impregnated or covered externally with elastin, and that we are dealing with fibres of collastin. Further, it is clear, that some of the thick fibres inside consist of basophilic collagen, and have

taken up elacin at their margins; they stain, with this triple colour, bright red at the borders, distinctly brighter than inside, and they correspond on side view, in respect to their colour, exactly to the elacin fibres described above.

Here, on account of the instructive cross sections of the coarse fibres, the development of collastin and collacin may very easily be demonstrated. Naturally, this triple stain gives very gaudy pictures, in which brown, red, blue and mixed fibres are closely intermingled, though sharply defined from one another; but that, here in the small space, a rationally combined staining method shows such sharp differences on apparently similar fibres, is the best proof of the chemical nature of the degenerative changes. Simple physical alterations (swelling, drying, etc.), might induce certain differences in colour, but never so sharply in such a small space. If, after the study of these combined stains, we now return to the simply stained preparations, we understand the two originally strange conditions, namely, first, that, in comparing the collagen and elastin preparations, the fibres in question looked remarkably alike, were present in the same amount, and ran in the same direction—for with these stains, we see, not only collagenous and elastic fibres, but also, without distinction, although more faintly stained, elacin, collacin and collastin. And secondly, we now see the reason of the abnormal position of the collagenous and elastic fibres, which do not, as usual, interlace, but run almost parallel; for most of them are degenerated, and the *elacin* fibres have lost their previous elasticity (*cf.* chapter: Striæ), and, following the movements of the skin, have gradually become horizontal and parallel, for they are stretched, but cannot return to their original position.

To sum up, we have in this piece of myxœdematous skin, a widespread degeneration of the connective tissue frame-work, which alone suffices to explain the sodden, cushion-like appearances. But there is something more remarkable, which appears to be related to the often-mentioned presence of mucin in the lymphatics. If we stain with polychromic methyl-blue, and decolourise in glycerine ether mixture, we see, especially in the swollen, succulent, quasi-œdematous parts of the papillary body, but also scattered in all other parts of the skin, peculiar, a-morphous, cloudy, veil-like, or definite, and then perfect crystalline formations, which have taken the characteristic rosy colour of mucinous bodies. On decolourisation with tannin, these structures are more apparent, but they take the blue colour. They lie free in the skin, but only rarely follow the course of the spaces and fibres, rather tending to cross them, perpendicular to the surface. Crystalline formations are more frequent than the unformed, and usually show, in their long axis, a small, dense body, with toothed or

brush-like, finer rods or prisms attached, so that they form feathery crystals. They may often be followed, connected by their fine processes, over large areas of the skin. As a rule, one meets in almost every well-stained section, about half-a-dozen large crystals.

The unformed structures of the same nature are very difficult to describe. They most nearly resemble the flat, veil-like surroundings of certain very large mast cells (v. Neuro-fibroma). They often lie in broad bands, along the epithelium of the surface and the hair follicles.

In contrast to these, the small number and size of the true mast cells is very remarkable. The sections must be very well stained before any are found. Some consist of a nucleus, with a halo of scattered granules.

Then we see on the epithelium of the surface, the hair follicles and the coil glands, another remarkable appearance, which is possibly connected with the presence of this infiltrating substance. The lymph spaces of the epithelia are filled with very fine granules, which, with the last mentioned stain, show a blue colour, and, since the epithelia usually remain passive, have probably got here from the connective tissue.

The specimen, unfortunately, was got from the stage of healing, and was too small to follow these promising appearances further; and I look all the more to a speedy confirmation of them for the pathology of Myxœdema of the skin, as they will no doubt cause further investigation of this interesting chapter.

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2. With loss of substance.

Striæ.

By striæ, I understand, in contrast to idiopathic linear atrophy, and to accidental linear pressure atrophy of the skin, simply those *persistent linear thinnings* of the skin, of simple traumatic origin, *due to excessive tension*, which develope on the abdomen, mainly and regularly from pregnancy, from ascites, obesity, the different intra-abdominal tumours, and, further, from the same transient causes of excessive tension, on the extremities, breasts, etc. Their direction is always at right angles to that of greatest tension, and therefore they form a series of parallel rows. The epidermis is changed, folded, more trans-

parent then normal ; the colour, after the tension has ceased, is at first reddish violet, and when the tension disappears, become greyish white, bluish, or mother-of-pearl colour.

Küstner, who first examined the structure of Striae, found a true loss of continuity in the cutaneous tissue, without more closely determining the share of the individual elements. In a large work, Langer opposed him, stating that the collagenous tissue showed no lesion of continuity, but only suffered from displacement and altered conditions of tension. The epidermis he also found intact. Troisier and Ménétrier confirmed Küstner's view, in a certain sense, by recognising that the elastic tissue underwent a complete local lesion of continuity. They found the epidermis simply thinned, and its connection with the cutis loosened, and this they attributed to the disappearance of the papillæ. The displacement of the collagenous bundles took place only in the cutis, not in the subcutaneous tissue. The bundles, which normally cross at acute angles, all took the direction of the pressure, and became almost completely parallel, and this displacement ceased sharply at the border of the striae, where the conditions were again normal. From the tension and displacement, the connection of the collagenous bundles gave way ; the parallel-fibred tissue of the striæ therefore appeared rarefied, and thus different from the dense tissue of a scar. The blood vessels were also displaced in the direction of the tension. The most striking changes were found in the elastic tissue, which was distinctly increased in the neighbourhood of the striæ. The few coarser fibres run in the direction of the tension, and leave between them, large spaces, containing either none, or very fine elastic fibrils. In the neighbourhood of the striæ, the elastin is increased, the rolled up, coiled, or cork-screw ends of the ruptured elastic net of the striae being closely packed together. Otherwise, these authors found no changes and noted no differences between fresh violet, and old mother-of-pearl striæ. The original dark colour was ascribed by Hebra and Kaposi to escapes of blood during the development of the striæ ; but they do not show the play of colours of hæmorrhages, and Troisier and Ménétrier found no trace of them. Küstner attributed the change of colour to the greater transparency of the striæ at the commencement, the deep blood vessels being better seen through them than through the surroundings, while the transparency was again lost by thickening of the cutis and epidermis ; a view with which Troisier and Ménétrier agree. Except for rupture and mechanical displacement, the authors could find no change in the elastin itself.

Philippson found the same characteristic mechanical changes in the papillary body and the epithelial ridge system of the striæ, as these authors found in the elastic tissue. Here, also, there was a persistent

displacement, which was produced directly and solely by the excessive temporary tension. At the margin of the striæ, the regular ridge system of the surroundings showed an elongation of its meshes in the direction of the force. Then there disappeared, in succession, those trabeculæ of the ridge system which were perpendicular and oblique to the direction of force, their epithelia being required to cover the enlarging surface. The papillary body was flattened in the same degree. Finally, there only remained, inside the striæ, those ridges which were exactly in the direction of the tension. These never completely bridged the striæ, and were widely separated from one another. The papillary body inside the striæ was still more completely flattened out than the ridge system.

I have several times had the opportunity of examining the striæ of pregnancy, and can confirm and amplify the statements of Troisier and Ménétrier, as to the partial, local disappearance of the elastic tissue. I find, according to the degree of change, and the breadth of the striæ, the appearances very differently developed in the elastic tissue. In the smallest striæ, there are only a few fibres inside the cutis which are really torn and retracted; most of them are only elongated, and form, with the equally stretched collagenous bundles, alternating horizontal bands. With a good stain and a high power we see that these thick bands consist mainly of bundles of very fine elastic fibres, which, in places, spring from a thick bundle, like the bristles of a broom from the handle, and continue the direction of the thicker fibres. There is therefore a breaking down of the coarser fibres into very fine fibrils. These fine fibres are, in parts too numerous, and in general too thin, to be identified with compressed, ordinary, small elastic fibres of the skin. Some fibres are always torn, and are found loose or twisted up at the borders of the striæ. But this excessive action is limited to the cutis proper. Neither in the hypoderm, nor, as I can affirm, in the papillary body, is there any tearing of the elastic fibres.

In more distinct striæ, a central area is almost, but never completely wanting in elastin. The tear inside the cutis proper is broader above than beneath, and has, in general, on section, the form of a trapezium, whose larger basis is upwards. But, even here, the continuity of the papillary fibres is preserved; there is only a moderate stretching of the net, so that, from the well-known garland-formed loops, there developes a flat, undulating, and, in the centre, perfectly flat net, which radiates towards the middle line of the striæ. Here, in the centre of the section, the elastic terminals of the papillary body, coming from opposite sides, meet, and show the line of maximal tension more exactly than the broad and gaping tear of the coarser fibres beneath. The relatively perfect preservation of the papillary fibres is evidently owing

to the fact that the elastic net here is normally capable of considerable movement, and, while losing its original form, escapes complete rupture. It is exactly the same appearance as in the papillary body and in the epithelial ridge system, both of which have reserves to fall back on, and are merely flattened out by the tension.

In addition to these mechanical changes of the elastic tissue, there are structural ones, which become apparent with a specific stain for elacin. All the striæ which I examined, contained, in greater or less amount, elastic fibres, which were transformed into elacin, stained only faintly with elastin stains, but deeply with basic ones, and had lost their sharp, tendrillary bendings. They consequently exactly correspond to the elacin fibres which are found in senile skin, and for this reason alone the striæ cannot be regarded as simple mechanical deformities of the skin, but must be looked on as true regressive metamorphoses. That this is accidental, appears to me to be excluded, because it occurs in persons of middle age, and the striæ themselves always contain more elacin fibres than the marginal parts, in which the accumulation of the torn elastic fibres takes place. Now and again we meet, in the centre of the striæ, with very thick, swollen elacin fibres and small elacin clumps, stained deeply with basic colours, just as a few isolated elastin clumps are visible near to the rarefied elastin net.

It is of special interest to note, that the elacin fibres which run through the striæ, are physically different from the elastin fibres. They are not torn through and separated in the centre, and consequently not rolled up and accumulated at the margin, but, like the collagenous fibres, are simply stretched, and, in excised preparations, only slightly wavy. It therefore appears to me certain, that the elacin fibres have lost some elasticity, and have become inelastic and plastic; and elsewhere, where they are present in abundance, in senile skin, in scars, in colloid degeneration and in Myxœdema, we shall be able to recognise, histologically, a diminution in cutaneous elasticity. In virtue of this physical difference between elacin and elastin, the elacin fibres are collected inside the striæ, and the elastin fibres outside.

What occurs in the over-stretched skin is, therefore, that the collagenous and elastic fibres are maximally stretched in one direction, and arrange themselves parallel to the direction of tension; the enclosed organs, especially the coils, are also elongated in this direction, and diminished vertically. Since the outer layers of the skin are necessarily more stretched than the more central ones, the stretching increases from within outwards; it is only slightly noticeable in the panniculus, and increases steadily inside the cutis, up to the papillary body. Here it again suddenly diminishes, in small striæ it may completely disappear, for the papillary body allows a good deal of

stretching without rarefaction. Therefore the greatest changes are found inside the cutis proper. The collagenous and elastic fibres are loosened; but while the former are separated from each other by widening of the lymph spaces, the elastic fibres retract to the sides of the striæ. Many of the elastic fibres withstand the tension without tearing, but undergo other regressive metamorphoses, some of the thick fibres breaking up into brush form, while in others the elastic substance is converted into inelastic elacin.

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Ulcers.

Ulcers are peculiar, chronic losses of substance of the cutis. So long as a loss of substance, induced by trauma, gangrene, &c., does not granulate, it is no ulcer, nor is it if it granulate well. Only when it attempts to fill up by granulation, but scarring is hindered by breaking down of the granulations or deficient cornification, do we call it ulceration. Ulceration is, consequently, *granulation tissue hindered in its typical involution.* So long as breaking down tumours (*e.g.*, carcinomata, sarcomata, gummata) show no tendency to commencing scarring, so long as no granulations are formed, there is no ulceration. Only if granulations develope over the specific tissue, do we speak of ulceration, *e.g.*, of syphilitic or leprous ulceration. In this case, the ulcer consists of an altered granulation tissue, unfavourable to scarring, which is here surrounded by a shell of specifically altered tissue.

As we have seen in connection with scarring, normal healing of any loss of substance depends on the accord and proportionate development of three different histological factors: 1, *the budding of young capillaries,* with the transformation of connective tissue into a cellular granulation tissue; 2, *mitosis of the surrounding epithelium,* with formation of epithelial ridges and union of the epithelium to the connective tissue; and 3, *the secondary shrinking of the vessels,* with the formation of collagenous substance in place of the granulation tissue. It is thus clear that an interference with normal healing may occur by an interference with one or more of these factors, and may therefore appear differently. There may be added external and internal disturbances, independent of these factors, which interfere with the otherwise favourable conditions of healing, and in this way give origin to the formation of ulcers. Practice, depending partly on etiological considerations, partly on the external appearance, has distinguished an enormous number of different forms of ulcer. Histological investigation shows, that certain appearances are constantly

repeated, and that, retaining these factors in our minds, we may make a simple histological division of ulcers into a few large groups.

I distinguish two main groups: 1, ulcers which depend on *essential disturbances, i.e.*, disturbances of the above factors of healing; and 2, those which depend on *accidental disturbances.* The former group has been much more carefully investigated than the latter, largely because it comprises the so frequent ulcers of the leg, which provide ample material.

In the first group, arranged in order of frequency, are: 1, the cornified ulcers (Ulcus hyperkeratodes, callosum); 2, the anæmic (U. anæmicum, atonicum, asthenicum); 3, the hypertrophic (U. fungosum, Caro luxurians); 4, the hæmorrhagic (U. hæmorrhagicum); and 5, the œdematous (U. œdematosum).

Many more ulcers than is generally believed, prove, on investigation, to be partly *cornified*, and *premature* and *excessive* cornification is a frequent hindrance to healing. Such are very large ulcers on skin sclerosed and fixed to bone, with pale greyish-red or greyish-yellow, very firm granulations and scanty secretion, which are pretty widely surrounded by hard, swollen, pale, smooth borders; also ulcers with overhanging borders on movable skin, and with no tendency to granulation; further, small, apparently almost healed ulcers, whose base is quite smooth, greyish-white, and almost completely covered by the callous borders; and finally, the *pressure ulcers*, which develope after long lying, or under splints over bony protuberances, and in which a horny ring, movable, but without any tendency to healing, encircles the smooth, greyish-white ulcer.

In all these cases we find, as the most important symptom, that the removed borders of the ulcer are clothed, on the under side as well as on the upper side, by a pretty thick, well cornified prickle layer, sending epithelial ridges into the cutis. The callous appearance of these borders consequently depends, not, as is usually assumed, on the fibrous character of their connective tissue, but is simply the expression of a complete wreathing with cornified epithelium. By surrounding the borders of the ulcer, it sequestrates them, and makes them completely incapable of covering the ulcer with epithelium, however long and firmly they lie on the base of the ulcer. Instead of this, there is an attempt at cornification at a deeper level, by the outermost border of the ulcer, which is covered by the edge. In very small ulcers, especially if the granulation be moderate, this is successful, and one then has the completely cornified, healed ulcer, which, however, always retains the form of the ulcer, *i.e.*, overhanging callous, greatly cornified borders, and a deficiently cornified base. But usually, and on all large ulcers, this cornification underneath the border does not take place, and only a small peripheral rim of the base of the ulcer is cornified, while the middle of the ulcer produces very irregular granulations. The epithelial covering, which, under the border strives

to cover the granulations, is a feebly nourished, so-called "granulation epithelium" (Friedlander). It is distinguished from the normal epithelial border of granulations, in ordinary scarring, by the absence of mitosis. It is simply pushed on from behind, it never advances independently. The epithelia are broad and flat, show no cylindrical layer and no true cornification; they have not the power of forming ridges and of furrowing out new papillæ. Thus there is no sufficient fixation of the epithelial border on the granulations, and the result is, that slight disturbances, bleeding in the granulations or œdematous swelling, suffice for the destruction of the weak epithelial covering. The cause of the cornification of the border, which induces the arrest of scarring, is almost always a deficient granulation of the base, which again may have its local or general cause. Thus the epithelial border is driven to follow a false path downwards. Where the granulations spring up well at the commencement, but where, in their transformation into collagenous tissue, on account of the indurated character of the surrounding skin, they cannot reach up, they flatten out all the more, and assume a particularly firm character. In these cases, the regular cornification from the border is arrested, and the epithelial edge tends downwards. In this way develope the very large, indolent, callous ulcers. In pressure ulcers, the pressure favours, on one hand, the hyperkeratosis of the borders, while, on the other hand, it does not permit the proper formation of granulation, and thus, in both connections, it tends to the development of an over-cornified ulcer. In rare cases, these ulcers are kept up by inappropriate application of keratoplastic remedies, which have the same action on epithelium and granulation, as mechanical pressure.

In contrast to all other forms of ulcer, in these, the border alone, by its excessive cornification, is the true hindrance to healing. Its removal is sufficient in all cases to induce at once the long-wished-for healing. Unwittingly, the treatment by cauterising the walls with nitrate of silver or nitric acid has followed this lead, the caustic destroying the erring epithelium. But removal of the borders is more rational, for their epithelium can be used for transplantation.

The rapidly appearing marginal cornification of many ulcers is frequently favoured by the fact, that the traumata or necroses, which lead to the ulcers, partially destroy some of the follicles around the border. Then from their bases, the prickle layer grows in the same way, and covers the under side of the border of the ulcer; just as in superficial destruction of the follicle, the surroundings are covered by a growth of new surface epithelium. The formation of hair is arrested. I have not yet been able to determine that the coils take any part in the cornification of the under side of the edge.

The *anæmic ulcer* is externally like the cornified, but flatter, as if dried up. It developes from persistent limitation of the flow of blood, more frequently from local than general disturbance. The walls are smooth and hard, but never overhanging, and pass into a base covered with a very thin layer of granulation. There is almost no discharge, and the base is dry, reddish-grey or even whitish, and insensitive.

The border of the anæmic ulcer shows a thin layer of pointed epithelium, cornified or dried up, without mitosis, and it sends only feeble ridges downwards. It adheres firmly to the flat granulations, and at places is dried up into a thin, deeply staining crust. The granulations are poor in cells, their vessels small and scanty; the superficial vessels especially are very feebly developed or altogether absent, while the collagenous substance reaches nearer the surface than usual. The deficient supply of blood appears to delay healing, mainly because it interferes with the new epithelial growth, and mechanically hinders the advance of the epithelium by drying, while it leads to a premature formation of collagen in the granulation.

The *hypertrophic ulcer*, "proud flesh," the Caro luxurians of older authors, occurs where the loss of substance is too luxuriantly replaced. It occurred more frequently during the period of strict antisepsis than before or since. The hypertrophic granulations are elevated from 1-5 millimetres and more over the level of the surrounding skin, and are enclosed by a thin epithelial border, which, instead of covering the granulations and depressing them, often cuts into them from the side, so that they project beyond the wall. Otherwise, the appearance of the granulations is perfectly healthy, indeed luxuriant, and the delay in healing appears inexplicable.

The borders of these ulcers provide the most perfect contrast to the borders of the over-cornified ulcer. A thick, well-formed layer of prickle cells reaches close up to the granulations, and partly sinks into them in the form of ridges, partly forms a thin layer over the granulating wall. The epithelium is sometimes regularly cornified, sometimes a horny layer with rod-shaped nuclei is formed. But no thick horny layer is ever formed, as in the cornified ulcer. The granulations themselves are typical; they have wide, perpendicular blood vessels, plasma and spindle cells in abundance, and, deep down, a horizontally arranged young collagenous tissue. But their luxuriance does not correspond to the feeble development of the epithelial border, and here we have the explanation of the deficient tendency to heal. It is usually sufficient to change the form of application, and, instead of dermatoplastic antiseptics, containing oxygen or chlorine (especially sublimate), which favour the growth of the granulations, and delay mitosis and cornification of the epithelium, to use keratoplastic and reducing agents (Resorcin, Ichthyol, Sulphur, Zinc gelatin), in order, at

once, to re-establish the balance between granulation and epithelial growth. Here, the delayed growth of the epithelium, which lags behind the formation of granulation, is answerable for the delay in healing. Once the granulations have got beyond the level of the skin, it becomes ever more difficult for the epithelium to cover them, and at the best we have a hypertrophic scar. Treatment has consequently to be directed to the flattening of the granulations, and in this connection the old-fashioned repeated application of caustic was of some benefit. But a flattening of the granulations alone is not sufficient, if we do not at the same time favour the growth and the cornification of the marginal epithelium. The reducing agents (*e.g.*, sulphur) effect both purposes at once.

The *hæmorrhagic ulcer* is a frequent type of the *varicose* ulcer; many varicose ulcers of the leg develope from hæmorrhagic ones, but, usually from the predominance of one of the three factors of healing, they are transformed into one of the other forms of ulcer. The hæmorrhagic ulcer is a bluish-red to blackish-brown, shallow or deep loss of substance, whose scanty granulations are permeated by small hæmorrhages, or filled with blood like a sponge, and at whose base the varicose vein lies, more or less exposed. Marginal cornification is absent, or descends to the insufficiently developed granulations, and we have at best a very thin, fragile, breaking down scar, if active granulation has not previously altered the type of the ulcer. Usually a limited but total necrosis of the skin lying over the varix accompanies the development of the hæmorrhagic ulcer, and this is why the smaller ulcers often appear as if punched out, and the larger ones show polycyclical forms.

I have not yet been able to examine a hæmorrhagic ulcer. But partly from our knowledge of the anatomy of varix of the skin and its surroundings (*q.v.*), and partly from the clinical symptoms of the ulcer, we may very well assume a deficient granulation on the one hand, and deficient epithelial mitosis on the other, while the cornification does not seem to suffer under the influence of blood stasis and hæmorrhage in the tissue, any more than does the conversion of the granulations into fibrous tissue, where these have been formed. The examination of such ulcers must show whether this view is correct. They would further be most appropriate material for the study of the formation of cutaneous pigment.

The *œdematous* ulcer is, in contrast to the hypertrophic ulcer, less firm and vascular. It is found along with general or local œdema of the neighbourhood, and is distinguished by pale, transparent, moist, soft, spongy granulations, projecting over the level of the skin, and by an inactive epithelial border.

Partial œdema of the granulations is very frequent, as is not remarkable when we reflect that most of them are ulcers depending

on the influence of stagnatory or hypostatic hyperæmia. These œdematous parts are found almost entirely on the surface of the granulations. The delicate collagenous tissue found here, is separated by wide lymph spaces, swollen and colloid, and contains a few small plasma cells, large spindle cells, and a good many white blood corpuscles. Where the œdema is more severe, the granulations swell in their upper parts, so far as they are not occupied by firm collagenous tissue; the blood vessels are partly compressed, partly dilated, but never, as usual, surrounded by sheaths of plasma cells. All the cells are poor in granular protoplasm; the processes of the spindle cells may be followed a long way into the colloid, transparent connective tissue. Especially distended is the upper angle of the granulation, and it is very evident that the young epithelium cannot get a footing on it, for usually with a much less degree of papillary swelling, we have loosening of the whole epithelium from the cutis. Since, clinically, the œdematous ulcer does not develope as such, but is developed from healthy granulations, or other forms of ulcer, we may assume in most cases, that an already formed border has been thrown off by the swelling granulations. After these latter have for some time projected over the level of the skin, we have the same difficulty in healing as in the hypertrophic ulcer.

The second group of ulcers, in which the healing factors are all present, but are hindered in their activity by *accidental* conditions, comprises mainly infectious processes, present before the formation of the ulcer, or afterwards added. The tertiary syphilitic ulcer of the leg represents the type of the former, and in it we often find together, several or all of the forms described in the first group. We usually find, in the centre of these large, horse-shoe-shaped ulcers, swollen, fresh-looking granulations, separated by atonic, sunken, and œdematous, swollen areas, and, on the one side, bordered by sharp, nibbled borders, parts of which are cornified and project like tongues, while, from the opposite side, the scarring extends, like the *hilus* of a kidney, into the centre of the ulcer. We can hardly suppose that the local factors of healing would vary so remarkably in such a small space, and would delay scarring on the greater part of the ulcer, while they permit it on one single spot. The rapid alteration in the appearance of the ulcers under specific treatment shows, with certainty, that all the local conditions for granulation and cornification were present, and that only the influence of the specific granuloma, which surrounded the ulcer like a shell, or, to speak more precisely, the specific affection of the vessels supplying the ulcer, delayed scarring. From the commencement of treatment, onwards, all the factors fall into line. The horse-shoe shape of the ulcer disappears, and it heals often in a surprisingly

short time, in spite of the apparently unfavourable external conditions. How treatment acts on the individual factors of scarring, we do not presume to say; this is a good field for experimental pathology.

We can better estimate the influences which external infectious agents exert on the ulcer. The growth of streptococci on the surface leads to inflammatory, erysipelatoid swelling; of the diphtheria bacillus, to the formation of diphtheritic membrane; and of unknown organisms, to different forms of moist and dry necrosis. In all these cases of *inflammatory, irritated, diphtheritic* and *gangrenous ulcers,* the primary effect is not that of these germs; but we are dealing primarily with some form of ulcer (*e.g.*, varicose), or with normal granulations, which are specifically altered, to a greater or less degree, from without. The further behaviour of the ulcer, and its healing, usually depends only on these secondary infections.

We have finally to note a peculiar form, the *erethic ulcer*, which, both clinically and anatomically, is a secret whose solution, like so many secrets, we must look for in the future nerve pathology of the skin. It is a small, very sensitive, smooth, dark red, thin layer of granulations, which is margined by a flat, often loose epithelial border, and resists all treatment. Usually, after temporary improvement, there is increased periodical pain, and a rapid enlargement of the ulcer. Sometimes some simple treatment leads to scarring, but we get no explanation of the previous obstruction to healing. It is possible, that in these ulcers we have some nervous disturbance of the skin, but none such has yet been recognised. The cases which I have treated give me the impression that cornification is only delayed by some change in the granulations, which hinders the adhesion of the epithelium. The nearest comparison is that of an idiosyncrasy of the skin to drugs.

Plantar Ulcers.

The Perforating ulcer.

This incurable, dreaded form of pressure ulcer was first described by Vesigné (1852) as *mal perforant du pied*, and has since been mainly regarded as the expression of a tropho-sensory disturbance (Fischer, Duplay, Samuel and others). Only recently has it become known that these ulcers may appear under very different conditions (in healthy people, along with other nervous disorders, in leprosy, etc.), and that the clinically uniform appearance and the difficulty in healing, are induced by the frequent combination on the sole of the foot, of several unfavourable factors, viz., the body weight, which is quite as injurious as the pressure on other localised ulcers, diminished sensibility (*e.g.*, in lepers), other pathological and senile changes of the skin (endarteritis, sclerosis), and finally, the penetration of irritant foreign bodies.

The trouble usually commences as a yellowish, afterwards blackish callosity, whose seat of predilection is found under the metatarsal bone of the great toe, then under the heel, and more rarely on other parts of the sole. Suppuration, perhaps traumatic, leads to the throwing off of the callosity, and we see underneath, a deep, either crater form or sinuous loss of substance, whose overhanging callous borders do not permit of healing. The granulations are either pale and firm, and discharge a thin fluid secretion, or they are dark red, uneven, ragged, and covered with stinking secretion. Trophic disturbances and neuritic symptoms in the neighbourhood are sometimes present along with the ulcer, but not invariably.

Winiwarter found the papillæ in the neighbourhood of the ulcer enlarged and directed towards the centre; thus the thicker ridges are thinned, and become cord-like. The horny layer around is thickened, and is swollen at the borders into a horny wall, which presses the callous borders inwards, and, hindering scarring, lies directly on the granulations. The granulation surface is thinned, permeated by hæmorrhages and pigment, and is covered on the surface with a layer of reticular hyalin. The cutis beneath the granulations is sclerotic and tendinous, with thickened sclerotic vessels, some of which show endarteritic changes, while others are thrombosed. The callous borders may induce atrophy of the cutis and of the bone beneath. Their removal alone, without simultaneous improvement of the base of the ulcer, the blood supply, the formation of granulation, and the avoidance of further pressure, is not followed by healing. This histological description by Winiwarter would apply to most pressure ulcers with overhanging borders. The crater-formed plantar ulcers possibly show other peculiarities.

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Necrosis, Gangrene.

While limited necrosis is a pretty frequent occurrence on the surface of the skin, and often enough added as an unwelcome complication to other cutaneous affections, necrosis of the whole corium is one of the rarer and more serious occurrences, and indicates some serious injury. There are two forms of injury, and therefore we distinguish, anatomically, two distinct forms of cutaneous necrosis.

Either the cutaneous tissue is *direetly destroyed* by some external trauma, of physical or chemical nature, or it perishes, *indireetly*, by a *sudden* or *gradual* cutting off of the blood stream. In the former case,

we expect different appearances, according to the physical and chemical characters of the destructive agents, according to their relations to the individual constituents of the skin, and according to the intensity of their action. This subject, whose study is of such practical importance therapeutically, pharmacologically and forensically, is, so far as concerns histology, almost untouched. The indirect necroses of the skin, from shutting off of the blood stream, also form, etiologically, a very multiform group, but it has, anatomically, a much more uniform character, on account of the invariable cause of the necrosis, the complete anæmia. While, in the former group, we expect very interesting and different changes in the structure of all the elements of the skin, most of the indirect necroses are distinguished by the similarity of their changes. The differences are to be attributed to the differences in the processes which have caused the cutting off of the blood. Especially important is the *capillary stasis*, which is to be regarded as, in most cases, the cause of gangrene of the skin. Next come vascular spasm, and the anæmia which it produces in a few but definite cases of cutaneous necrosis. Embolism and thrombosis of large vessels very rarely lead to gangrene of the skin, and usually only when the underlying tissues, fasciæ, muscles, and especially whole extremities undergo necrosis.

And we cannot make the widespread process of obliterative inflammation of the vessels answerable for the appearance of necrosis, although this is often done, especially in syphilitic ulcerations. We are familiar with many affections in which this process is extreme, and in which the altered skin, in general, shows no tendency to necrosis, so that in those cases where such a combination is found, some other cause must be at work. For example, in Sclerodermia, endarteritis is extreme, but necrosis of the skin very rarely occurs, and only when protuberances of bone, and flexed joints, from within, or the nails of contracted fingers, bandages or such, from without, act upon the skin. The relative innocence of this form of vascular degeneration is due to the fact, that it rarely goes on to complete obliteration, and invariably attacks only some of the vessels of a region, so that others make up the deficiency. For, while the capillary region is mainly nourished by single arteries, the free communication of the cutaneous capillaries always keeps up a certain amount of circulation.

Nor is the atheroma of the larger cutaneous arteries, in old people, sufficient cause for the senile gangrene of the toes, for the atheromatous changes in the temporal artery are never followed by necrosis. In these cases, analogous or other changes in the heart are responsible for the gangrene, which developes from a stagnatory or hypostatic

hyperæmia of the extremities, which gradually goes on to capillary stasis of the skin.

The so-called *neurotic gangrene* of the skin, whose main types are the *acute decubitus* (Samuel, Charcot) (*q.v.*), and the mutilation of neurolepers, is also very problematical. In the latter, it is undeniable that the possibilities of trauma, due to anæsthesia, play an important rôle in the development of necrosis. But an influence on the circulation of the skin of nervous disturbance, excessive stagnation forming the basis of capillary stasis, is quite possible, and a vasoneurotic gangrene from vascular paralysis, as a contrast to the necrosis of vascular spasm, may very well occur.

While all these causes relate to organic or functional changes of the cutaneous vessels, and the nature of their action is very much in the dark, the form of cutaneous gangrene caused by mechanical lesions of the vessels, presents no difficulties. We have first the different forms of *pressure gangrene.* Necrosis occurs most readily from pressure on the skin from within; very naturally, for here the larger subcutaneous vessels are first encountered, *e.g.*, by the prominence of joints in contractures, by dislocated bones, fragments of bone, concretions of uric acid, tense abscesses of the ends of the fingers, etc. The ensnaring cutaneous ring in paraphimosis also undergoes such a constriction necrosis.

Pressure necrosis, like constriction necrosis, makes the skin entirely anæmic, parchment-like, dry, and yellowish white, and also thins it considerably. Most familiar is the strangulation furrow on the neck; in the snaring off of large tumours, and in the bites of animals which have not led to tearing of the skin, it also occurs. And severe squeezing of an already stretched part of the skin, which is deficient in fat, or lies over some bony process (tibia, olecranon, patella), may directly lead to complete necrosis (primary compression necrosis, Winiwarter). In all these cases the vessels of the skin are not only emptied during the pressure, but they undergo a sort of welding, and when the pressure is removed are unable to take up the blood again. Therefore pressure most certainly leads directly to necrosis, when the supply of blood into the vessels is completely arrested, *e.g.*, during the anæmia which accompanies every stretching of the skin, and so we find in almost all of these cases, a combination of compression and stretching. The tangential, widespread stretching from within, *e.g.*, over the condyles, always represents a radial, punctiform pressure on the skin, and so on. Only in the most acute pressure necrosis, is the welding of the fibrous constituents of the skin also so marked, that it aids in preventing the recovery of the compressed area of skin. In all these cases, the cutaneous tissue, in virtue of its elastic and firm qualities, stands the

stretching and pressure well, and the necroses which develope are solely to be ascribed to the permanent welding of the blood vessels. So that most simple necroses are really indirect, from interference with the circulation.

Like this accompanying anæmia, a complicating œdema also favours traumatic compression necrosis (*e.g.*, œdematous scrotum, prepuce), and for the same reason, the more complete shutting-off of the blood from the compressed vessels. The panniculus, on the other hand, the thicker and more fatty it is, opposes the development of simple pressure gangrene; the natural pressure areas of the body (soles, buttocks, thighs) are all supplied with a thick fatty cushion. The existence of a panniculus hinders any over-stretching by its inextensibility, as its yielding does an excessive compression of the skin, and thus there is not the absolute anæmia which is necessary for the simple traumatic pressure necrosis. And we see that tight clothes and bandages produce decubitus, in healthy persons, mainly in the non-fatty skin over bony prominences (tibia, condyles, backs of the feet and ridge of the nose), while a ring on the fatty first phalanx may cut deep, without producing cutaneous necrosis. It is owing to this that the fatty hypoderm is much less liable to pressure necrosis than the cutis, although every bruise is accompanied by the rupture of numerous fat cells; it is not easy for pressure anæmia to develope in the vessels of fatty tissue.

As frequent as the simple pressure gangrene, is the *hypostatic pressure* gangrene, the ordinary decubitus, the bed-sore of old people and acute and chronic invalids. Here also it is in those thin, non-fatty areas, that the cutis, caught between bone and bed, and long exposed to the weight of the body, first shows pressure gangrene (sacrum, ischium, spinous processes, iliac-spines, condyles), but pressure areas are also established on the fatty regions (buttocks, heels), and finally especially at those places where constant irritation is added by decomposing secretion (vulva, penis, anus). Thus we see that the hypostatic pressure gangrene has no such simple genesis. It is not the pressure alone, but rather the diminished circulation of the patient, and the hypostasis of the skin, which lead to gangrene. The pressure may indeed be as slight as that produced by the body weight, and yet hypostasis developes. It is also those areas which are lowest, which tend to gangrene. But that, in these large hypostatic regions, only those areas are affected which are directly and mostly compressed, is owing to the fact, that pressure paralysis of the cutaneous vessels is added to the hypostatic stagnatory hyperæmia, and thus a maximal stasis is induced.

Consequently, the appearances of the skin in hypostatic pressure gangrene are quite different from simple gangrene. There are formed

deep red or bluish-red spots, which, when observed under the diascope, at first disappear, but later remain yellowish-red, on account of the escape of blood serum, and, according to circumstances, are covered with a dry, brown, leathery scab, or with vesicles and a superficial, macerated, grey or dark grey slough, which, when it falls off, leaves a deep ulcer, with dark red, hyperæmic borders.

Hypostasis is therefore the main element in decubitus, equally important, if not more so than pressure, for the place of the latter may be taken by other disturbances of the circulation, or by the action of decomposing secretion. It is consequently not the general marasmus of these individuals, as such, which is to be regarded as the ultimate cause of ordinary decubitus, but rather the occurrence of peripheral hypostasis (from diseases of the heart and vessels, weak heart and vascular paralysis in typhoid, cardiac weakness in old people and chronic invalids, and vascular paralysis associated with compression of the spinal cord, and other diseases of the central nervous system). Hypostatic pressure gangrene is therefore a necrosis, the result of capillary stasis. The so-called neurotic, *acute decubitus* differs from the ordinary, only in its rapid development, and the insignificance of the external injuries, but it shows the combination of the same external and internal causes, and is probably no more distinguished anatomically than clinically, from the hypostatic pressure gangrene.

We have to distinguish from ordinary decubitus, the much more serious form of *progressive pressure gangrene* or *progressive gangrenous decubitus*, which—especially in septic and typhoid diseases—commences as an ordinary decubitus, but, with putrefaction of the secretion, attacks the subcutaneous tissue, and leads to very great loss of substance. Here there is undoubtedly added a new factor, which causes the extension of the gangrene, and this is probably the growth in the skin of some necrosing organism.

In addition to pressure, a mechanical lesion of the cutaneous vessels developes from *drying*. Normally, the skin is completely protected from drying, by the greasy basal horny layer. If this is absent, and the circulation is normal or more active in the papillary body, there is no danger of drying; but there is, if, at the same time, the circulation is, for any reason, slow (anæmia or venous hyperæmia). Then, very superficial erosions, "scruffings," hardly noticed, lead to the formation of a necrotic scab, which embraces the papillary body and even the sub-papillary vascular net. This extends, by drying and shrinking of the former, and consequent stasis, into the most superficial circulation. Such necroses are not uncommon as accidental complications of dermatoses, which do not otherwise lead to necrosis. Especially in the dependent parts of the body, and in individuals with weak

hearts, do these superficial necroses develope as the result of loss of the horny layer. It is well known that pedunculated lobules of skin, if they dry at their apices, regularly undergo gangrene. As, in general, simple loss of water does not interfere with the integrity of organic substances, and very often in lower organisms drying serves to preserve the chemical structure under unfavourable conditions, we must not in all cases ascribe the necrosis to the drying of the tissue as a whole, but especially to the drying and obliteration of the blood vessels. The blood stream can no more resume possession of the dried-up vessels than of the tissue welded by the pressure, and necrosis always developes.

We have therefore to consider, as the simple main forms of indirect necrosis of the skin, those which develope—

1. from capillary stasis,
2. from vascular spasm,
3. from simple pressure,
4. from drying,

and in conclusion, as the most important complicating form,

5. progressive gangrene.

A.—*Indirect Necrosis of the Skin.*

1. Necrosis from capillary stasis.

Capillary stasis, as an appearance of independent pathological significance, was first recognised by v. Recklinghausen, it having been previously looked upon as a manifestation of inflammation, and therefore not sufficiently estimated. Clinical observation of most cases of indirect, so-called spontaneous gangrene, teaches that necrosis is usually induced by a more or less complete stasis in the cutaneous vessels. The skin is thin, spotted and reddened, cold and often insensitive; the erythema has all along a bluish, livid tone, and there suddenly become apparent, usually at small areas, especially if some slight injury has occurred, dry, black, firmly adherent scabs or vesicles, with sanguineous contents. In the most favourable cases, healing takes place under the scab; usually we have prolonged ulceration, and often an advancing dry mummification or moist gangrene. The type of these ordinary cases of spontaneous gangrene is the so-called *senile gangrene* of weakly individuals, in whom it is usually located at the points of the toes. Here usually several causes combine to make the stasis complete and the necrosis inevitable: heart weakness, hypostatic hyperæmia, and external cold. In one such case, v. Recklinghausen found hyalin thrombosis of the cutaneous arteries, which had led to a widespread stasis in the skin. He assumes that prolonged contractions of the cutaneous arteries led to the formation of unusually widespread, hyalin

coagula, which, as the stream slowed, blocked the way. In view of the importance of the case I give it fully.

> An otherwise healthy rag-sorter, æt. 73, had often suffered from slight frost-bite of the feet. She developed gangrene of the toes of both feet, and died suddenly, after the gangrene had extended above the ankle and had never demarcated. The cause of death was an embolism of the pulmonary artery, from thrombosis of the right heart. The left heart, the aorta and all the large arteries of the legs, were free from coagula, but all the veins of the leg, from the cutaneous veins to the venous trunks of the thigh, contained recent, secondary thrombi. "Fresh sections of the necrotic skin showed numerous plugs of colourless, shining, almost homogeneous substance, many of them with blunt branches and a cylindrical, hunchbacked shape, so that they appeared to be casts of the lymph vessels. After hardening, their nature was clear ; the plugs were limited to the blood vessels, they were clothed at both ends and also at their sides by red blood corpuscles, and were seated in the small arteries of the subcutaneous and the deep cutaneous tissue, more rarely in the stratum papillare and the vascular loops of the papillæ. Only in the nail bed, could numbers of capillary loops, plugged with hyalin masses, be observed. The hyalin masses appeared quite homogeneous, free from nuclei and granules, and only occasionally were they slightly streaked, or composed of shining, thick trabeculæ. Only a few obstructed the whole vascular lumen ; many lay along the wall, especially those thrombi which extended from the larger arteries into their branches, and, throughout almost their whole length, they were separated from the walls by a layer of red blood corpuscles. Structural changes were not found in the arterial wall. The blackish blue colour of the skin, especially of the toes, corresponded to an over-filling of all the vessels with blood, especially to a great dilatation of the capillaries and the small veins, while the wide subcutaneous veins sometimes showed a connective tissue thickening of their walls, especially of their inner layers. Finally, there were marked hæmorrhagic infiltrations, both of the papillary layers of the nail bed and of the subcutaneous fatty lobules, and along with them a running together of the red blood corpuscles inside the capillaries and the venous vessels of these parts, so that the blood columns began to form a homogeneous but always blood-coloured mass, probably a secondary stagnatory thrombosis."

These observations, and the very plausible explanation of v. Recklinghausen, open to our comprehension a probably large series of cases of spontaneous necrosis, which appear after marked diminution in the calibre of larger cutaneous arteries, for they show the bond between them, in persistent hyalin coagula. But they by no means include all cases of senile gangrene, especially not those in which cardiac weakness and hypostatic hyperæmia precede the necrosis, though they probably include those cases of gangrene which are induced by prolonged arterial spasm, especially those of *ergotism* and *frost-bite*.

> In the necrotic combs and tongues of cocks poisoned with ergotin, v. Recklinghausen also found hyalin coagula, and similar deposits in the walls of the arteries, while the capillaries and veins were only distended with red blood

corpuscles. Here also the explanation appears very plausible, that severe contraction of the arteries has led to the formation of coagula, and this again to stasis. Grünfeld has since confirmed these observations in Kobert's laboratory. Whether these observations on cocks are completely applicable to human ergotism is, of course, not definitely certain, but very probable.

The histological nature of frost-bite, also, is but little known. One thing only is certain, it is not rightly regarded as an inflammation. It belongs, from its nature, to the regressive disturbances of nutrition, and comes nearest to the gangrenous processes here described.

Frost-bite.

In contradistinction to burning, freezing induces no primary textural changes in the firm constituents of the cutis; it is one of the indirect necroses of the skin. In our method of frozen sections this has long been familiar; a recognisable rupture of the elementary constituents by thawing of the ice, does not usually occur, unless in freezing we go to an abnormally low temperature, and the thawing is done by warm water. The only thing that is seen, now and again, on freezing œdematous skin, is an unusual distension of the lymph spaces. The primary changes, which are to be regarded as the causes of all later inflammations, are consequently limited to the fluid constituents of the skin, the blood and lymph.

The slightest degree of frost-bite is usually—aiming at symmetry with the degrees of burns—described as a hyperæmia; chilblains are sometimes placed here. Neither correspond to true freezing, as we have seen in the chapters on stagnatory hyperæmia and angioneurosis. Chilblains always indicate a pathological, abnormal skin; persons who suffer from perniosis, have added, under certain circumstances, the group of symptoms called chilblain. But even the stagnatory hyperæmia, which may be produced on every healthy skin, especially of the extremities, by excessive cold, is, so long as there is only hyperæmia, to be regarded, not as an inflammation, but as a vasomotor disturbance. At first, by contraction of the vessels, the resistance is mainly in the peripheral circulation, and if this is ultimately overcome by increased cardiac action (rubbing, friction of the skin, or warm applications), a stagnatory hyperæmia takes the place of the stagnatory anæmia, which, if the arterial system is more rapidly dilated than the venous, leads to œdema.

Strictly speaking, we only have frost-bite when a partial freezing of the most peripheral vessels, with their contents, occurs, for which the previous frigid anæmia, with vascular contraction, is an important predisposing factor. In freezing with the ether spray, we can very

easily note, by the suddenly appearing chalky-white colour, the point where the regulating mechanism of the vessel ganglia no longer acts, and the skin stiffens into a mass of ice. This familiar experiment teaches us, better than the slightest spontaneous frost-bite, *e.g.*, of the point of the nose or the big toe, that even complete freezing of a piece of skin may take place without danger and without inflammation, if it be not too prolonged. Since we know, on the other hand, that every freezing of the blood is accompanied by a solution of red blood corpuscles when the freezing blood rapidly thaws, we must conclude that this of itself does not produce inflammation.

In nature, however, the conditions are rarely so favourable as in the application of the ether spray. Here, with the persistence of the cold, there is usually a period, in which the primary freezing of the blood and the lymph are contemporaneous with the secondary reaction of the partial vascular paralysis of the skin. The latter is then not white and completely frozen, but, according to the amount of blood in it, greyish-red to dark blue; rapid and complete recovery of the circulation, as when the ether spray is stopped, does not occur; the temporary arrest of the circulation becomes a permanent obstruction.

The evidence shows that the stagnation of blood, accompanied by dark red, violet, or bluish-black staining of the skin, which appears as the reaction to the primary freezing of an area of skin, and usually extends pretty widely over the surface of the frozen tissue, is a true stagnatory hyperæmia, *i.e.*, that it is accompanied by necrosis in the blood vessels, and diminished rapidity of the stream. The skin then becomes doughy, and is usually covered with large, monolocular vesicles, which have clear or blood-coloured serous contents. The vesicles correspond to the most stagnated, darkest areas of skin, and have no direct relation—as in burns—to the application of the severest cold.

Wherein consists this constant hindrance to the stream, which occurs after freezing? So far as I know, there has been no anatomical investigation of human tissues altered in this way. Since the venous stagnation persists, even when the skin is artificially warmed, it cannot be that frozen blood in the vessels prevents the circulation. The next most likely thing is to assume, with Sonnenburg, that, during the primary freezing, thrombi are formed in the permeable peripheral blood vessels, which outlive the freezing and induce the subsequent conditions of stagnatory œdema and vesicle formation. Probably the arterial hyalin thrombosis found by v. Recklinghausen, plays a part. In favour of this are the observations which Kriege made, under v. Recklinghausen's directions, on the ears of rabbits, which were more or less frozen under the ether spray.

Kriege found that even temporary freezing produced thrombosis in the small cutaneous arteries, which he regarded as the "fine granular thrombosis" (of v. Recklinghausen), or as the "blood plate thrombosis" (of Eberth and Schimmelbusch). If the freezing is continued, it is followed by a "white thrombosis" produced by leucocytes, and finally by a "hyalin thrombosis." The hyalin developes partly from leucocytes, partly from the vascular endothelia, these cells swelling up, and becoming shining and gradually a-nuclear. This hyalin thrombosis induces secondary, scattered necrosis in the connective tissue, which chiefly affects the emigrated leucocytes and the collagenous tissue. The latter shows disappearance of the fibrillary marking, and swelling into coarse hyalin trabeculæ, which are beset with small, shining drops, and large, hyalin fragments, the former being hyalin escaped from the cells, the latter degenerated leucocytes. As the degeneration goes on, we have a hyalin change of the vessel walls, which commences with the musculature of the media, and converts the blood vessels into homogeneous bands, and a formation of free hyalin nets in the lymph spaces of the œdematous tissue, and even hyalin necrosis of the lower prickle layer. The observation of Kriege is of interest, that, after unilateral section of the sympathetic in the neck, the hyalin degeneration was twice as great on the side operated on as on the other. Though Kriege (like Samuel) regards the œdema which follows the freezing, and the slight leucocytosis, as an inflammation, his observations show that the inflammation only plays, if any, an unimportant rôle in the appearances of frost-bite, since arterial thrombosis leads to stasis, œdema, degenerations of primary tissue, and gangrene. The accordance of these factors with the clinical appearances of frost-bite on the human skin justifies the conclusion, that in examining it we may expect similar appearances. I consider it quite unnecessary to extend the definition of inflammation to this process.

If we assume such a widespread hindrance to the stream in the frozen area, the other appearances are easily explained. From the stagnation, at many points complete stasis developes, according to the degree of freezing, and the most superficial region, comprising part of the papillary body and the epidermis, becomes necrotic. There are formed on the bluish-red skin, brownish-red, parchment-like scabs, which are thrown off, leaving flat, bluish-red, sensitive ulcers, which heal with superficial scarring. If we regard this vasomotor disturbance as the earliest degree of frost-bite, we may regard the complication of stagnation with œdema and vascular formation as the second degree, and the third, as that when superficial necrosis of the skin is added.

We must not forget that vesicular formation in frost-bite of the second degree developes quite differently from that in burns of the second degree, in that neither inflammatory changes of the epidermis nor reactive inflammatory changes are present. This distinction will no doubt be established by the histological investigation of these vesicles. All the deeper necroses of the whole skin in frost-bite of entire limbs, we may put together, as a fourth degree of frost-bite. They appear as moist suppurating, or dry mummifying gangrene.

If we survey the whole series of changes which take place after frost-bite on the skin, we must admit that the frequent analogy drawn

between burns and frost-bite cannot be maintained. The one is a true inflammation, probably induced by the burnt products of the tissue, the other is a regressive disturbance of nutrition induced by the stoppage of blood.

We must ascribe to the *fibrin thrombi* a similar effect as to the hyalin thrombosis of the cutaneous arteries. They are found over large areas of the skin, and appear in numbers in a short time, while individual ones may give rise to no disturbance. Such an acute and widespread separation of fibrin in the arteries or veins of the skin, only occurs in the infectious processes whose agents secrete coagulative toxines. Among the first are Erysipelas and spreading Phlegmon, then many of those inflammations which lead to necrosis, such as Anthrax, Carbuncle, Noma ; but for this very reason it is, in individual cases, difficult to separate the necrosing effect of the fibrinous plug in the vessels, from the primary necrosis of the cutaneous tissue, which is the direct result of the immigration of the organisms. At least in many cases of gangrenous Erysipelas, we have, along with fibrinous thrombi of the cutaneous arteries, a widespread stasis in all the capillaries and small veins, which cannot be without influence on the acuteness and intensity of the necrosis. Nor must we forget, that the necrosing influence of micro-organisms may be exerted on the cutaneous tissue, without dilatation and stasis in the capillaries (as in glanders).

Following this form of gangrene, comes a whole series of accidental necroses, in those affections of the skin which do not usually lead to gangrene, such as Erythema, Zoster, Syphilis, Variola, Vaccinia. The thorough investigation of these cases should increase our knowledge of the factors which convert inflammation into necrosis. Here, also, v. Recklinghausen has recognised, in certain cases, as in the capillaries and veins in small-pox, hyalin thrombi. I had the opportunity of examining a gangrenous prepuce with a hard chancre, the gangrene being apparently caused by a slight degree of phymosis. The most striking phenomenon here, was a widespread fibrinous coagulation inside the skin, which was full of syphilitic plasmoma. Further, it was so œdematous, that, on superficial observation, the dry character of initial sclerosis was almost overlooked, and it looked like a soft chancre. Closer investigation, however, showed that it was a typical sclerosis, distended by œdema. But there was no coagulation in the vessels, corresponding to that in the tissue ; there was only great stasis. Both the plasma cells and the large spider cells around the sclerosis were rounded, and, by partial washing out of the protoplasm, converted into large, pale cells. I could not find any trace of secondary organisms.

Another cause appears to be at the bottom of the capillary stasis which leads to *diabetic gangrene*. In diabetes, the cause of a whole series of cutaneous affec-

tions is, beyond doubt, the abnormal composition of the blood. In many cases, the sugar-containing lymph of the skin only forms a particularly good medium for immigrated organisms; *e.g.* the frequent furuncles, carbuncles, and paronychiae of diabetics. In other cases, the sugar-containing urine prepares the epidermis for them, *e.g.* eczema of the genitals, balanitis and vulvitis. But there are diabetic dermatoses which are produced directly by the sugar as a reducing and dehydrating agent; such are Anhydrosis, Pruritus, Urticaria and Gangrene.

Diabetic Gangrene.

There are, of course, in old, weakened diabetics, cases of gangrene which are in no way distinguished from other cases of spontaneous gangrene, except that, in general, they have a greater tendency to advance, and a graver prognosis. But there is a specific diabetic gangrene, in the sense that all accidental, minute wounds, such as bruises, cuts, scruffings, especially on the feet and legs, very readily undergo gangrene, and further, certain forms which have as yet only been described in diabetes.

Thus Rosenblatt published the case of a patient with diabetes, who died of tuberculosis, and where, in addition to ulceration of the mucous membrane of the whole intestine, there were multiple cutaneous necroses. They developed from petechiæ on the under extremities, were the size of pin-heads to lentils, and were covered by brown, hard, smooth scabs, reaching into the cutis. These were dark-red down to the base. There were also found brown, pigmented spots, at the borders of the feet.

Investigation showed that the papillary body and the upper layer of the cutis were necrotic, and passed into a thick crust, partly adherent, partly loosened by epithelial undergrowth. Only at the border of the crust, was there found a moderate round-celled infiltration in the surrounding cutis. But there were no signs of hyperæmia and inflammation, nor of embolism or thrombosis. Both between the necrotic connective tissue bundles, and in the lower, well-preserved cutis, as far as the hypoderm, there were capillary hæmorrhages, and, in the connective tissue, diffuse, brownish discolouration, along with amorphous granular pigment. Cornification of the ulcer did not come from the epithelium of the surroundings, but from that of the coil ducts which were enclosed in the scab.

From these appearances, it is very probable that this was a case of hypostatic hyperæmia, with diapedesis of red blood corpuscles, which, under the influence of the diabetes, had gone on to stasis and necrosis of the sub-papillary vascular net. The deeper capillaries of the skin had permitted the escape of blood, but the circulation was preserved in them. Such a limitation of the necrosis to a small part of the superficial circulation, almost corresponding to a plane element, is a very

frequent observation in accidental, circumscribed necrosis, occurring in the course of other dermatoses of superficial character (*e.g.* in eczema of new-born children, in the region of the genitals).

> Kaposi has described a particular form of diabetic gangrene, which also had its seat on the leg, but had the form of serpiginously extending areas, with vesicular borders. In the centre, they passed into dry and moist gangrene, and finally into granulation. In another case, after twenty years of diabetes, the backs of the hands, and the fore-arms were covered with a papillary growth, like Syphilis vegetans.

In all these forms, in common with the ordinary form of diabetic gangrene, inflammation and pain is altogether absent, and necrosis is preceded by a livid discolouration of the skin, and bluish-black spots; in fact, the appearances of local asphyxia. Only in small, circumscribed areas on the extremities, is there drying and mummification. Usually, the scabs are moist, and surrounded by a bluish halo; discoloured vesicles filled with blackish serum appear, and the gangrenous areas run together into a slimy debris. In all these characters—the absence of congestive hyperæmia, the stasis, the formation of vesicles, and the soft flabby character of the sphacelus—this most common form of diabetic gangrene so much resembles those necroses of the skin caused by the excessive action of reducing agents (pyrogallol), that I must regard the view, originally put forward by Roser, that the gangrene was directly caused by the sugar, as probably right. Only here we have, in addition, determining factors, such as hypostatic hyperæmia, traumata and other dermatoses.

How the reducing agents, in large amounts, act on the circulation is not as yet histologically determined. To judge by the clinical appearances, there is capillary stasis, breaking down of red blood corpuscles, and saturation of the tissue with bloody serum. Whether this external analogy will be confirmed histologically, must be shown by the investigation of both conditions.

The worst form of diabetic gangrene, the progressive putrefying form, is, like all progressive gangrenes, to be ascribed to the addition of micro-organisms. In these cases, the subcutaneous tissue breaks down over large areas, but there are not, necessarily, appearances of inflammation.

Certain dyscrasias sometimes act in the same way on the cutaneous tissue, *e.g.* Mercurialism, Chronic Bright and Gout.

Finally, there is a series of dermatoses, which, commencing as capillary stasis, regularly go on to necrosis of small areas, and with which we are clinically but little acquainted, and histologically not at all. These are the cases of so-called *multiple cachectic cutaneous gangrene*, and *Zoster gangrenosus*. If, in the former, there is no external

infectious dermatosis, of unknown nature, and in the latter no self-infliction by hysterical persons, they may possibly be caused by multiple capillary stasis, from some internal cause. I recently examined a very typical case of this nature, and was able to investigate it histologically.

A woman, aged forty, previously healthy, was attacked three years before by an erysipelatoid affection of the front of the head, which healed, leaving behind it a ring-formed Alopecia (Ophiasis), and an elephantiasic swelling of the forehead. Since then, there had existed a universal disease of the skin, which was especially marked on the extremities and in the neighbourhood of the flexures (axillæ, groins, knees). There were, all over the skin, bluish, broad veins, forming irregular nets. In the nodes of this net, and elsewhere in the course of the blue cords, there arose, from time to time, reddish spots and flat papules, which became dark, and disappeared, leaving behind them pigment, or, becoming quite black and necrotic, were transformed into shallow, very painful ulcers, which healed very slowly, with smooth scars. I have described this case in the International Atlas, under the name : *Asphyxia reticularis multiplex.*

On examining a newly-developed, bluish red, not yet mummified spot, the whole prickle layer in the centre was found to be converted into a homogeneous, necrotic mass, with a few very much compressed nuclei. At the border of the spot, the necrosis ceased to extend, for, at the outer periphery, only a few basal prickle cells were seen transformed into homogeneous, round, non-staining clumps. The adjacent part of the papillary body was also necrotic in the centre, as far down as the sub-papillary vascular net, and it was also somewhat swollen. This vascular net was packed with red blood corpuscles, and some capillary loops in the papillary body showed completely agglutinated, red plugs. The cutaneous fibrillæ, surrounding these vessels, were stained yellowish. All the blood vessels which surrounded the necrotic area were not only dilated, but often surrounded, for a considerable distance, by inflammatory cell growth. The cellular areas consisted of small, rounded cells, and contained no plasma cells, and few mast cells or leucocytes. A broad cellular infiltration surrounded the coil glands, along with their ducts. The former showed simple dilatation and unrolling of the loops by the surrounding infiltration ; the ducts, very peculiar growths, with cystic formation (v. Syringadenoma). How far this latter appearance belongs to Asphyxia reticularis, I must leave undecided.

The cyanotic form of Raynaud's disease, the *local asphyxia* of the ends of the extremities, shows—like that just described—bluish-red to bluish-grey spots and swellings, which may disappear, leaving behind them pigment, or, becoming painful and often vesicular, may go on to superficial necrosis of the skin. According to the presence

of greater œdema or greater anæmia of the surroundings, this has the character of moist or dry gangrene. Until we have more precise histological data, we must regard it as probable that the necrosis, as in Asphyxia reticularis, developes on the base of capillary stasis. It thus forms a certain contrast to the anæmic form of Raynaud's disease, which we will now consider.

2. *Necrosis from Vascular Spasm.*

The most familiar example of a pure angiospasm, which may go on to necrosis, is *local syncope*, the anæmic appendix of *local asphyxia*, which may go on to this form (Raynaud), but may also appear as an independent affection of the toes and fingers, more rarely of the ears. In its mildest form, it is the so-called "dead fingers," a periodically recurring angiospasm, induced by cold. In its higher degree, it is a permanent, maximal anæmia of the ends of the extremities, which in some places, especially on the finger ends, invariably leads to circumscribed necrosis. Corresponding to the other characters of the disease, these have the form of a dry scab, which is only very slowly separated. These are the only cases where the purely functional disturbance of the cutaneous arteries can induce complete anæmia and consequent necrosis. From our knowledge of v. Recklinghausen's discovery of persistent hyalin thrombi after arterial contraction, it is possible, that here we have a similar thrombosis, with the difference, that it extends through the whole capillary net, and thus prevents its distension with blood, and capillary stasis.

The same doubt and the same alternative hold for ergotism, for the cutaneous necrosis in that condition, by no means always shows the local asphyxia type of necrosis, but also sometimes that of local syncope.

Further, in this group we must place the affection recently described by Besnier as *Urticaria necrotica*, in which small, superficial dry necroses appear on long persistent, urticarial eruptions.

3. *Simple Pressure Necrosis.*

We have not infrequently the opportunity of examining a "welded" skin, *i.e.*, a skin which has been markedly thinned by severe, rapidly acting pressure, as at the borders of compressed tumours. The circumstances are similar, but still characteristically different from the streak-formed necrosis of the skin, which is produced by the "mikrobrenner," and is described in the chapter on burns. The diminution in thickness is largely in the epidermis

and papillary body, least in the lower cutaneous layers. The horny layer forms a homogeneous band; the prickle layer shows closely-compressed cells, with rod-shaped nuclei, running parallel to the horny layer. The papillary body is also reduced to a thin, almost homogeneous band, with rod-shaped nuclei; but the papillæ are usually not completely obliterated, being only difficult to recognise, as thin, thread-like cones, placed obliquely between the compressed ridges. Since, with compression, there is almost always a stretching of the epidermis in a definite direction, these appearances are easily explained. The blood vessels of the papillæ and the sub-papillary vascular net are, as such, no longer present; somewhat darkly-stained rows of nuclei indicate their position inside the compressed collagenous substance. The extent of the gangrenous scab depends on the extent of this total compression of the blood capillaries. Usually, its under margin lies inside the under cutaneous layers. Where the compression is slight, the gangrene is almost always dry; where it is greater, and especially if the upper layers are removed, it may be moist.

As we see, the greatly compressed skin resembles that welding produced by dry heat, under slight pressure (see burn), in the closure of the vessels and the mechanical thinning of the epidermis and the papillary body. But there is neither swelling of the collagenous substance, nor the characteristic steam holes, and displacement of the prickle cells.

4. *Exsiccating Necrosis.*

That the preservation of the normal saturation of the tissue is necessary to the normal circulation of the blood, and that many stases in the superficial vessels, with consequent necrosis, are due simply to a rapid evaporation and drying, we know from experimental pathology. We certainly have here the same factor of a condensation of the blood plasma as in many other forms of stasis; but there is, in addition to this influence on the blood fluid, a specific action of drying, on the vascular walls of the capillaries, which opposes a continued resistance to the circulation, even if the inspissated and conglutinated blood cylinder has been long dissolved, and the causes of the exsiccation removed. Thus we are right in separating the necrosis due to drying, as distinct from the other necroses due to capillary stasis.

In the human skin, which is so well preserved from drying, this factor only comes into consideration if the greasy, protecting horny layer is removed, and at the same time the peripheral circulation, and thus the rapid replacement of the evaporated water is feeble. So we find in quite unimportant epidermic scruffings, in eczemas on the legs of old people, on intertriginous areas on the buttocks of weakly children,

a sudden drying attacking circumscribed areas, leading to horny deposits, black and hard, and quite different from ordinary crusts. They usually comprise the whole mummified papillary body.

As we see, drying alone is very rarely the cause of necrosis of the skin, but it readily combines with other necrotic tendencies, with hypostatic hyperæmia, anæmia and traumata, to bring about the arrest of circulation, which is already prepared for. Thus, in examining eczemas and impetigines of such persons dead from some intercurrent disease, we usually meet with small grangrenous areas. They appear, on the corpse, just like those parts which have dried up post-mortem, because bereft of their horny layer. But while on such, the rod-shaped, compressed nuclei of the dried-up and thinned prickle layer are regularly arranged, the cell margins distinct, and the papillary body shows no noteworthy changes, we find, in the places which have dried during life, the prickle layer run together to a homogeneous, horny mass, without distinct cell margins, and with stainable, but irregularly distributed, and deformed nuclei, and the superficial capillaries of the papillary body, with or without blood cylinders, taking the deep stain usually shown only by the dried borders of preparations. Sometimes only the upper border, together with some blood cylinders, is deeply stained, while the under border shows the ordinary stain. These appearances show, that, in the drying of unprotected skin, the capillary walls give up their water more rapidly than the surrounding cutis. They dry up and shrink, and are then probably lost to the circulation, for we know that we cannot cause animal tissue which has become dry and horny, to swell up again.

These superficial drynesses are found much more frequently in granulations and various ulcers, especially soft and hard chancres, than when the prickle layer is preserved. It is then not always easy to say, whether a simultaneous stasis has favoured the drying, or the drying has induced the stasis. In favour of the latter, is anæmia of the superficial capillaries; of the former, marked hyperæmia, with yellowish discolouration of the tissue around. The necroses produced by the drying up of the most superficial areas of the skin, always, of course, lead to the formation of thin, dry scabs. All these forms of cutaneous necrosis have certain histological peculiarities in common, which, before we go on to gangrene complicated by infection, must be shortly described. In necrotic scabs, a demonstration of the protoplasm is always difficult, often impossible, although in this point there are great differences between the moist and the dry, and those with or without marked stasis, and it very often depends on the rapidity with which the death of the tissue occurs. In many cases, neither cell margin nor a trace of protoplasm is recognisable in the epithelia and

cutaneous cells, in others the cell margins are faintly recognisable, but staining is unsuccessful. In most cases, the nuclei are much better preserved, and in the dry forms of gangrene retain their full staining power. The elastin is usually well preserved, at least I have always been able to stain distinctly, even the fine elastic fibres of the papillary body. The behaviour of the collagen is peculiar; it usually retains its structure unaltered, but its capacity for basic stains (*e.g.*, methyl-blue), usually slight, is increased. All these changes together give one the impression that some substance of acid reaction had combined with the necrotic tissue, and we must endeavour to discover whether such really is present in the necrotic areas. The perfect preservation of the elastin and the nuclein, the destruction of protoplasm, and the basophilism of the collagen, would then be very readily understood.

5. *Progressive Gangrene.*

In the unlimited extension of gangrene, we have sufficient grounds for assuming the addition of a parasitic complication, when we are dealing with a further extension in the continuity of the skin and the hypoderm. In gangrene of whole extremities, the advancing thrombosis of the large vessels sufficiently explains the extension of gangrene. But the ordinary cases of progressive gangrene which succeed to decubitus or ulcers of the leg, or develope from a circumscribed phlegmon, always indicate the addition of a specific, necrosing organism.

> I have only once had the opportunity of examining a gangrenous, decubital ulcer. The loose border was black for about one centimetre; on this gangrenous area, followed first a light brown gangrenous halo, and then a yellowish zone of about the same width, both still in the loosened cutaneous border. A fourth zone was formed by the not undermined, inflammatory red line of demarcation.

In the gangrenous zone proper, all the blood vessels, from the capillaries to the large subcutaneous ones, are filled and dilated, but no fibrinous thrombi are visible. On staining the collagenous tissue, which is unusually distinct, the stiff, injected vessels stand out very clearly. In the large vessels, the individual blood corpuscles are well preserved, there is no marginal arrangement of the leucocytes in the veins, and they are not increased in number inside the vessels. In some subcutaneous arteries, there is a distinct development of the endarteritic process; but if the lumina still gape, they are filled with red blood corpuscles; a proof that the necrosis is accompanied by complete paralysis of the vessel musculature. Cylindrical agglutinations of

blood corpuscles are found only in the smaller superficial vessels of capillary type, especially in the broader venous branches, and in the capillaries of the papillary body.

We have therefore, here, a complete stasis in all the vessels of the skin, which can neither be caused by thrombosis, nor by an anæmia accompanying the endarteritic process. The endarteritis must so far be regarded as a predisposing condition, since the energy of the circulation in that area is diminished, slowed, and the amount of blood irregularly distributed.

With a protoplasm stain we see that the protoplasm has completely disappeared. The small vessels and capillaries of the skin are more or less densely surrounded by proliferating perithelia, but we only see their nuclei. All the more evident are the mast cells, around the vessels of the skin, though they are paler than usual, and therefore appear much larger. If we observe them with a high power, we see that, even here, the protoplasm has perished, and the persistent mast cell granules surround the nucleus as a scattered, irregular mass. The elastin is as well or better preserved than the nuclein of the connective tissue. One may follow the finest fibres of the completely necrosed papillary body, and also the fine fibres of the coil glands, and the coarse net of the blood vessels, just as well as in the normal condition. In contrast to this, the collagenous tissue is considerably altered; the fibrillary marking has disappeared, the collagenous trabeculæ retain basic colours more firmly than usual, and towards the surface and at the borders, can hardly be decolourised after any stain. The completely necrotic papillary body, which usually contains no nuclei, has lost its epithelial covering. Only here and there between the papillæ, are there still adherent remains of the necrotic prickle layer, and where these are found, they are held together by a smooth and apparently unaltered horny layer. The epithelia of the coil glands are also completely necrotic, have broken down, and little but remnants of nuclei are seen in the centre of the empty tube; or the centre is filled with a non-staining mass, with stained remains of the nuclei. The epithelia of the ducts and follicles are well preserved, and some hairs project unchanged out of the necrotic skin. Finally, with a methyl-blue stain, we find in the papillæ, especially those still clothed with epithelial remains, and most abundantly inside the necrotic epithelial masses, numbers of short, thick bacilli, whose ends are very prominent. These form connected, branching processes in the lymph spaces, where they are held together by a mucoid mass. From the larger areas, faintly staining, scarcely recognisable remains extend through the lymph spaces of the adjacent cutis, and must be regarded as dead. Large, but mostly dead masses of the same bacilli surround the necrotic coils, and extend

into the deeper layers of the cutis. The bacilli neither resist acids nor iodine.

The brownish zone following the gangrenous area, so far as concerns bacterial development, represents the acme of the process. Here, the lymph spaces of the papillary body are densely packed with bacilli, which form a knotted net-work, and between the cutis and the loosened epithelium, a shell-like layer, finally penetrating through the epithelial lymph spaces into the latter, which still contains well-stained nuclei. Then we can distinctly see that the complete necrosis of the epithelium is definitely due to the permeation by bacilli. Only towards the gangrenous centre, where the bacilli are dead, does the staining power of the nuclei of the epithelium also disappear. From here, the bacilli extend into the subcutaneous tissue, and have a second maximal point in the coil glands themselves, whose epithelium becomes necrotic and breaks down, like the surface epithelium, under their influence. The gangrenous area is very unlike the halo, in relation to the behaviour of the vessels. The subcutaneous veins show that the leucocytes are somehow attracted there, for most of them show marginal arrangement of the white, and diminution of the red blood corpuscles. In the transitional veins, we find diapedesis going on. Leucocytes flock to meet the bacilli in the lymph spaces, and thus the cutis is permeated by a fine net-work of them, but there are never large abscess-like collections. They die, lose their protoplasm, and the remains of the nuclei mingle with the nuclei of the perithelia and other connective tissue cells. The elastic tissue is of course as well preserved as in the gangrenous area, the nuclei, mast cells, and collagenous tissue rather better than there. But the protoplasm of the cutaneous cells has already perished.

The yellowish external zone of the broad halo shows the outposts of the bacilli, and therefore the commencement of the necrosis. The bacilli penetrate between the surface epithelium and the sub-papillary vascular net, in the lymph spaces of the papillary body, exactly like the streptococci of Erysipelas. Beyond them, a peculiar œdema may be recognised in the surface epithelium, which undergoes parenchymatous swelling; in some of the prickle cells of the deeper layer, the granular protoplasm is washed out, so that with a simple methyl-blue stain, both its system of fibrillæ and its inter-cellular bridges appear isolated, and show a crossing net-work, in which the nucleus lies as in a basket. The immigration of the bacilli into the epithelium takes place later. Streams of leucocytes advance through the branched lymph spaces, against the superficially seated bacilli — the middle cutis and the coil glands show no bacilli—and here the emigration from the sub-cutaneous vessels is more marked than in the central portion of the

halo. The subcutaneous fatty tissue is closely permeated by leucocytes, and liquefies under their influence. It is quite clear, that, from the point where the bacilli immigrate into the skin, downwards, the cutis is loosened from the tissues beneath it, so that the whole necrotic area only lies loose, and in the centre, merely shows a few rags of fatty tissue on its under side. In this peripheral zone of gangrene, the elastin, nuclein, and collagen are well preserved, as is the protoplasm of all the coil glands and most of the surface epithelium; the disappearance of the protoplasm begins first in some, mostly superpapillary prickle cells, and in the cutaneous cells. The blood vessels show Cohnheim's type of inflammation: a typical leucotaxis.

The zone of demarcation, which, during life, is reddened, but in alcohol preparations appears normal, only shows a dilatation of the vessels, and a leuco-serous inflammation, which commences simultaneously in the deep and superficial vascular nets. Except for an œdematous swelling of the cells, the epithelium is normal, but there is a considerable immigration of leucocytes, much more than on the surface of the gangrene itself. The cutaneous cells and perithelia are not increased in number.

Summing up these facts, we have to distinguish three different processes—(1) a process which precedes the necrosis, which can no longer be exactly recognised, but must have consisted of a stasis with inflammatory irritation, for thus only can the multiplied perithelia of the gangrenous area be explained; (2) the immigration of bacilli, through a tear in the epidermis, into the papillary body; and (3) the opposing immigration of leucocytes and serous exudation into the subcutaneous and cutaneous tissue. The last two processes meet in the gangrenous halo; in its inner zone the bacterial development culminates, in its outer, the leuco-serous inflammation. Both appear to exert mutually opposing influences. The leuco-serous inflammation leads to the demarcation of the gangrene, and eventually to the elevation of a bullous marginal wall. In my case, there was softening of the prickle layer, and elevation of the epidermis, without any proper bullous formation. The death of the bacilli is brought about chemically, by the exudation, and not by phagocytosis. In the gangrenous area itself, most of the bacilli are already dead.

From these observations, and especially in view of four points—(1) that bacillary immigration precedes the necrosis, (2) that its course corresponds exactly to the advance of the clinically recognisable gangrene, (3) that the bacilli in the necrotic centre are mostly dead, and (4) that they are the only organisms in the dying tissue—I cannot refrain from ascribing to them the character of necrosing bacteria, consequently of specific "gangrene" bacteria, and I do not believe that

they represent saprophytic, putrefactive organisms. They are at least distinguished from the ordinary bacteria of putrefaction, by their not resisting iodine.

B.—*Direct Necrosis of the Skin.*

Direct necrosis of the skin has been, as already noted, very cavalierly treated, although it is possibly *the* field of experimental pathology which permits the most definite and easily estimated conclusions in regard to practice. The nature of many common injuries, and their distinction from other dermatoses, as well as the therapeutic application of substances used in dermatology, are made much clearer by the exact histological investigation of their action on the cutaneous tissue in concentrated form, *i.e.*, of the different forms of cauterisation and necrosis of the skin.

> There have been, of course, many experiments made in this connection ; but only in the form of experiments on the delicate, transparent membranes of cold-blooded animals, and on the ears of the rabbit. Only the latter experiment (Samuel) permits of general application to human skin. Samuel used more or less concentrated acids and alkalis, chloride of zinc, tin, antimony, phenol, cantharidin, croton oil, arsenic, etc., and simple scalding. According to the intensity of the action, he found, either a simple inflammatory hyperæmia, or along with that, a formation of vesicles, and superficial necrosis, or, finally, two zones of necrosis, a central dry scab, surrounded by a discoloured halo, sometimes with vesicles. Reckoning from the maximal change, Samuel distinguished in the necrosis, three zones : that exposed to the most severe action, the *central gangrenous area*, an intermediate zone, surrounding this concentrically, the *gangrenous halo*, and a peripheral zone of *inflammatory demarcation*.

This division may be very well applied to human pathology, for, in burns and cauterisation, this zone formation is usually repeated ; though now and again, in a minute necrosis, the gangrenous area and the gangrenous halo run together. There correspond to these three areas, the zones which necessarily follow from direct necrosis : the central one, where the caustic has completely and immediately destroyed the skin, the most peripheral one, in which the reaction of the skin is in the form of inflammatory congestion, and one between the two, in which these two extremes meet. But it is at once evident —at least judging by the chemotactic theory of inflammation—that there are necroses which possess no line of inflammation, for the substances which produce the necrosis (*e.g.*, concentrated phenol) have only a negative chemotactic action. In such cases the gangrenous area is only surrounded by a gangrenous halo, in which the effect of the caustic slowly disappears. On the other hand, all those necroses of the skin which are caused by an agent whose action is only transient

and local, will show no gangrenous halo, but only an inflammatory halo of reaction, such as that found in burns. Thus we know something more, in the histological sense, of that special form of death of the skin, and are able to explain, histologically at least, this form of necrosis.

I have twice been able to recognise a direct traumatic necrosis of the skin, as such, by histological examination, the cases having previously been regarded, from the false statements of the patients, as cases of neurotic, indirect gangrene. In both cases I could exclude burning as the cause of the scab, from the absence of positive symptoms in the collagen and elastin. But I do not care to determine more exactly the nature of the irritant, since we have no exact knowledge of the histological changes produced.

We do know a little about *carbolic acid gangrene*. Frankenburger recognised that the circulation was arrested by the development of capillary thrombosis, and thus absorption of the poison from the skin was prevented. I have investigated the influence of concentrated carbolic acid, especially on lupus skin, and will describe the changes which are seen on the healthy surroundings of the nodules.

After one application of concentrated carbolic acid, there developes, inside the epithelium, a perfectly horizontal line of scab, which, on repeated applications, slowly, and always in layers, advances downwards. In the cauterised horny layer, the nuclei again appear in rod form, but when the cauterisation is frequent, they disappear again in the completely homogeneous, detached horny membrane. At the same time, there is formed in the prickle layer, a zone of reaction, which, for a time, paralyses the further influence of the caustic. The altered prickle layers lying next the horny layer, undergo cloudy swelling, but without reticular degeneration, and form a thick, œdematous, cellular cushion; while the younger layers, especially the epithelia of the ridges, proliferate rapidly, and further, show a general prominence of the nuclear chromatin, in the form of coarse, multiform threads and granules. When the scabbing reaches into the cutis, stasis appears in the blood capillaries, without emigration of leucocytes taking place around the alternating red and white thrombi. The collagen loses its fibrillation, becomes homogeneous, and unites inseparably with the protoplasm of the connective tissue cells, whose nuclei remain well preserved. After a continuation of this action, the dead cutaneous mass becomes more and more homogeneous, and there is no indication of the contours of the connective tissue bundles and vessels. Spaces appear in it in all directions, and it thus has a perforated, weather-beaten appearance. Some deeply-staining nuclear remains however always persist. This dry scabbing, which runs its course without suppuration or demarcating infiltration, may heal with a depressed

scar, the epithelium simply growing under the scab. Or there takes place, secondarily, in the neighbourhood, a moderate hyperæmia and inflammation, by which the scab is thrown off, and the loss of substance filled up by granulation.

Thus cauterisation with carbolic acid produces the type of a dry, sharply-margined gangrenous area, with a small gangrenous halo, and none, or very slight reactive inflammation. It is, further, well characterised by the epithelial changes described.

In this, and by the addition of more serous inflammation in the scabbed region, *cauterisation of the skin with clove oil* differs from carbolic gangrene. The direct action on the epithelium reaches only to the basal horny layer, but there occurs, indirectly, a marked change in the prickle layer, by the development of interstitial œdema, and the formation of purely serous vesicles, which show no leucocytic immigration. In the cutis, clove oil necrosis is never so sharply margined as carbolic gangrene. The clove oil does not advance in layers, but has a broad zone of diminishing activity. Here also the nuclei are well preserved, and the collagenous tissue, together with the protoplasm, is transformed into a homogeneous substance, in which splitting and fibrillation is more marked than in the case of carbolic acid. The cutis swells up and has a spongy structure. The circulation does not at once cease, but it does so gradually and completely. The soft, porous scab leaves, after it is thrown off, a flat œdematous ulcer. The application of clove oil does not, as a rule, lead to any noticeable inflammatory reaction of the surroundings; nor does it cause suppuration; but it has a very distinct serotactic action.

In future investigations, we must decide in each case, whether the changes found are the direct results of the caustic, or are indirectly due to reaction. Possibly there are agents, which, on external application, so injure the vessels, that the traumatic development of the necrosis is overlooked, and it is called indirect. v. Recklinghausen found, in a paraffin burn, where the white gangrenous halo markedly contrasted with the brown gangrenous area and the red reaction zone, almost all the capillary loops of the halo transformed into shining, solid, hyalin, sometimes thickened masses.

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B.—With Atrophic Conditions Predominating.

1. Simple Atrophies.

Atrophy of the Skin.

I have, by placing senile change of the skin among the degenerations, given expression to my conviction, that the changes recently studied under this name, mainly on the skin of the face, are not to be regarded as atrophic, but as degenerative. But Neumann distinguishes a simple senile atrophy of the skin from the other changes of old age, and so it is still questionable whether the individual elements of the skin do not, like the rest of the body, become limited in their nutrition under the influence of senility, and reduced in size and succulence, without there being any degenerative changes. The external appearance of the thin, flabby, folded skin of old people leads one to assume such simple atrophic conditions, solely due to senility; but which parts of the skin mainly suffer, in what order they grow old, and how the different regions of the body differ, are all unanswered questions. Certainly, the diminution in volume does not affect all the constituents in the same degree, and different parts in the same way, as the frequent occurrence of luxuriant growth of hair, increase in pigment, a well-developed fatty cushion along with a very much thinned cutis, or complete loss of pigment, the skin being otherwise well nourished, show. And in regard to cancer we have had pointed out to us, with a certain right, the relative youth and power of proliferation of epithelium, compared with connective tissue, in the skin of old age. All the constituents must consequently be separately and regionally examined, before we reach clearness in the matter, and only then will it be possible, histologically, to explain with any certainty, the varying appearances of aged skin.

The other causes which induce atrophy in other tissues, especially more acutely-acting ones, such as fever, hunger, nervous influences, gastro-intestinal disturbances, are not followed by any general atrophy

of the skin, but only by an atrophy of the fat. The fat cells lose part of their fat, and therefore their tense form; a fact no less remarkable because it occurs daily. Probably in these cases, the fat—as in the neighbourhood of inflammatory areas—is consumed more rapidly than it is replaced; but of this, and especially of the behaviour of the protoplasm of the fat cells, we have no accurate knowledge. In starving animals, Flemming found a proliferation of the protoplasmic parts of the fat cells, the so-called proliferative atrophy of fat, but I have not found this on the atrophied skin of patients, dead from febrile diseases. The possibility, therefore, that the emaciation is induced only by the want of a normal addition of fat to the panniculus by the fat producing glands, is not excluded; indeed, in emaciation from nervous influences (great mental activity, want of sleep, care) this is the only conceivable explanation.

The limitation of the supply of blood by endarteritic processes, by no means leads with certainty to atrophy of the skin, which is notoriously adapted, by the high tone of its vessels, to a very variable, and generally small supply of blood. The influence of obliterative endarteritis can only act in very rare cases, where it is persistently progressive, and attacks not only individual vessels, but all of them, in greater or less degree. On this extreme development of cutaneous arterio-fibromatosis possibly depend certain rare cases of progressive cutaneous atrophy in central nervous disturbances (tabes), which are accompanied by a sort of glossy skin of the extremities, and of which I have examined one case, combined however with senility.

> What the form of atrophy is in Paget's glossy skin, and in the trophic disturbances which (according to Weir Mitchell, Moorhouse, and Keen) appear after wounds of the nerves, we do not yet know. The inflammatory complications in the former, and the angio-neurotic symptoms in the latter, indicate that it is no simple atrophy, but more complicated processes, which lead to total degeneration of the skin. Unilateral atrophy of the face is a more typical example of atrophy due to nervous influences. But here also we have no accurate histological investigations, and in examining such cases we must, on account of their localisation on the face, be cautious in distinguishing simple atrophic cases of atrophy of the face, from Sclerodermia (morphœa).

So there only remains one distinct, general factor: *pressure.* There are, in this book, so many examples of pressure atrophy of the skin, that I may limit myself to a short summary. Pressure atrophy is best seen over slowly-growing, hypodermal or more deeply placed tumours, the layers of the skin being partly compressed from within outwards, by radial pressure and tangential traction, and partly thinned. The action of pressure is least in the fatty tissue. Those fat lobules which are not directly affected, retain all their normal structure; those which are compressed lose their fat, and their blood

capillaries are first transformed into a loose, cellular, then into a fibrous, almost a-cellular tissue, and finally combine with the connective tissue membrane of the tumour. The elastic substance completely disappears by atrophy and rupture, but only so far as the pressure reaches, and it usually accumulates in the neighbourhood. If the pressure proceeds from distended blood vessels, especially from varix, new elastic tissue developes all around; what factor causes the softening is not yet known, but I suspect the oscillation of the blood pressure. The collagenous tissue, on the other hand, shows, over wide areas, the influence of pressure and traction, for the fibres are plaited and interlaced. They are only stretched in *one* direction, and are first arranged parallel, then stretched, and finally very much thinned. At the same time, first the blood capillaries, and then the larger blood vessels and the spindle cells disappear. The papillary body is stretched into a homogeneous flat plate, and, correspondingly, the ridge system of the epidermis disappears, and the epidermis is reduced to a few layers of cells. Most of the blood capillaries being lost, there can be no successful resistance of the parts, but, if the pressure do not go on to necrosis, the skin may remain for a long time as a thin, fibrous shell. The enclosed organs are simply pushed aside, and they too undergo pressure atrophy. Here, as in varicose pressure atrophy, there is the exception, that the coil glands which do not directly suffer from pressure, often show signs of proliferation. The hair follicles are usually pushed aside, bent and thinned, and, if spontaneously shortened in casting the hair, remain shortened. Ultimately, the remains, becoming ever flatter and shorter, are taken up into the surface epithelium. The sebaceous glands atrophy very early, and are not nearly so long recognisable as the coil glands. The cutaneous muscles disappear in the completely atrophic skin, but are seen in the immediate vicinity, where they appear to suffer no more than the elastic tissue.

In the chapter on Striæ, we have already considered the atrophy of the skin which developes from simple tension without simultaneous pressure.

In addition to these symptomatic atrophies of the skin, we are familiar, from the reports of Buchwald, Touton and Pospelow, with an essential skin disease, atrophic in nature.

> The skin of the extremities is, in this idiopathic, diffuse atrophy, very much thinned, and quite inelastic over large areas, so that large folds are present even in rest, and the skin can be picked up in still larger folds, without their flattening out. Cold did not induce goose-skin. There is seen through the skin, a perfect net of subcutaneous veins, and when the limbs are dependent, all the smaller veins of the skin become evident. The skin is dry, does not sweat, and is not œdematous. Pospelow compares it to crumpled-up cigarette paper.

Buchwald found complete absence of the fatty tissue, general

atrophy, remarkable diminution of the sweat glands and hair follicles, and absence of the papillæ. The character of the connective tissue close under the epithelial border, is remarkable; it seems swollen, and contains numerous cell nuclei. These were partly collected in isolated groups, independent of the vessels, follicles and glands, partly arranged around these, and also scattered through the tissue. In the vessels and nerves there were no remarkable changes. The thickness of the whole cutis was 1·5 millimetres, of the epidermis 0·1 millimetre.

Pospelow found the skin, on section, extremely but irregularly atrophied, and about a fifth of its normal thickness. The oblique muscles were almost gone, only atrophic remains being found on the follicles. The horizontal cutaneous muscles (non-follicular muscles?) were infiltrated by round cells, thickened or atrophic; all the epidermic layers were thinned, and the prickle layers pigmented. The papillary body was flattened and its capillaries dilated. Arteries, lymph vessels and lymph spaces showed no abnormality, the veins were distended with blood. The hair follicles were very atrophic, the sebaceous glands slightly so, and the tunica propria of the coil glands was more delicate than usual. Pospelow found no changes in the cutaneous nerves.

This would indicate a pure atrophy, mainly of the collagenous tissue, cutaneous muscles, and probably also of the elastic tissue, although the authors do not note it. Future investigation must show whether it is a pure atrophy, and not rather, as the clinical appearances and the remarks of Buchwald about the sub-papillary connective tissue, and those of Pospelow about the muscles, indicate, a degeneration, leading to atrophy.

The atrophy of the female genitals (Kraurosis), described by Breisky, Janowsky and Ohmann Du Mesnil has not yet been histologically investigated.

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Atrophy of the Hair.

Atrophy of the hair, as a manifestation of general pressure atrophy of the skin, we have just considered. Seborrhœic Alopecia has been fully considered in the chapter on eczema, and we saw there that this disappearance of the hair is mainly to be attributed to a diminution in space, by the increase of the fatty cushion of the scalp. In favour of this is the fact, that seborrhœic Alopecia very rarely appears except on the scalp. Michelson has published such an exceptional case, but in it there was also syphilis.

> A silver worker acquired syphilis in 1879. A year after his last inunction in December 1881, with the appearances of a well-marked alopecia pityrodes, bunches of hair fell suddenly from his beard, then from the head, axillæ and pubis, so that there was soon total alopecia. His previously red hair was completely replaced in July 1882 by blonde.

On the bald areas, the mouths of the follicles were partly beset with dark points, which, when squeezed out, were seen to be rudiments of hairs, wreathed in portions of the prickle layer of the hair follicle. They represented the deeply-pigmented, loose ends of a shaft, which, instead of a normal cortex and medullary substance, only produced a brush-like collection of hair cells. In another case of *Alopecia pityrodes universalis*, Michelson also found most of the hairs surrounded by the prickle layer of the hair follicle.

That, where an abnormal size of the bony cranium is congenital or developes during life, or the scalp is abnormally stretched by other processes (operation scars, multiple atheromata, etc.), the seborrhœic process will lead all the more easily to wide-spread alopecia, is quite evident. So far, a limited hereditary tendency to seborrhœic alopecia cannot be denied. But there is another form of Alopecia due to seborrhœic catarrh, which is usually treated as an independent disease, Alopecia senilis.

Alopecia senilis et præmatura.

> The baldness of the head in old people is such an every-day fact, and has been so long familiar, at least in all civilised countries, that it is difficult to oppose the general assumption, that there is a direct connection between alopecia and senility of the skin. But as yet, a true *Alopecia senilis*, in the strict sense of the word, has not been anatomically recognised. Some have even gone further, and have assumed, along with general senile atrophy of the skin, a general alopecia; but it is only necessary to observe a number of healthy or unhealthy individuals who have passed their fiftieth year, to prove the contrary. Every epoch of life, puberty, the climacterium, senility, tends on the contrary to greater growth of hair, both in connection with the thickness of the hair in general, and in the places where, instead of lanugo, strong hairs are developed. That the female beard only begins to grow at the climacterium is well known,

and the appearance of unpleasantly thick hairs in the nose and ears of old men, and on the covered parts of the body, shows, even with complete greying, anything but a diminution in number and thickness of the hairs. Baldness of the head, therefore, in old people is a remarkable exception to the rule, and must depend on some special cause.

Since we now know that the alopecia which commences on, and is at first limited to the centre of the scalp, and from this in time extends outwards, is such an unfortunately frequent symptom of seborrhœic catarrh of the scalp, the question arises, whether possibly senile alopecia, this paradoxical symptom of senility, may not be simply an unrecognised Alopecia seborrhoica. This can be determined by clinical and histological investigation, by the former, if it be possible to exclude the commencement of an Alopecia senilis with seborrhœic symptoms, which I have not been able to do. Certainly Pincus, to whom we owe the first description of seborrhœic alopecia, and the introduction of the term *Alopecia pityrodes*, has shown by his statistics, that in senile alopecia there is a more rapid increase of all the symptoms : the absolute loss of hair, the relative loss of the uncut pointed hairs, and the hair thickness. But if Alopecia senilis should prove to be only a relatively delayed alopecia due to long-standing seborrhœic catarrh, this unimportant difference would be very easily explained. For, as we have already seen, definite Alopecia seborrhoica is only the expression of a gradually more difficult after-growth of young hairs ; consequently, if this appear first in old age, it would be more rapidly evident. This leads us on to histological investigation.

Pincus found the anatomical structure of the skin in Alopecia senilis, in its important particulars, just as in his Alopecia pityrodes. But the thinning of the cutis proper, compared to the hypoderm, was still more marked, as was only to be expected in general senile skin.

Michelson believes senile alopecia to be induced by changes in the blood vessels. He found an Endarteritis obliterans of the larger blood vessels, and a partial obliteration of the capillaries of the hair follicle. The epidermic structures atrophy, and the cutaneous tissues shrink. The hair follicles were diminished, and thus their mouths gaped, so that, on inspection, they appeared conical. They were mostly filled with loose horny masses, or lanugo hairs. The cutaneous muscles were widened, cloudy and fatty. Sebaceous and coil glands were unchanged in size and structure. Around the coil glands, there were often found areas of cellular infiltration, whose significance Michelson does not discuss. He says nothing about the fatty tissue.

From the examination of the bald scalp of old men, I can in general confirm this description. But I did not find the muscles fatty ; though where free fat was abundant in the cutis tissue, drops of it could be recognised, in osmium preparations, between the muscular bundles. The integrity of the glandular apparatus, indeed its increase in volume compared to the follicles, I also noted, and I could further determine a thickening of the panniculus, at the expense of the thinned cutis. In view of these observations, I feel unable to draw any definite

distinctions between Alopecia senilis and Alopecia seborrhoica, further than the simple differences of age. That endarteritis obliterans can cause no senile alopecia, and has no more a causal connection with senility than with many other results attributed to it, has already been stated, and moreover, it exists in many other conditions, which do not lead to baldness. Further, in my experience, it is no very prominent symptom in preparations, for it usually affects only certain vessels.

When I had become more familiar with the senile changes of elastic and collagenous tissue, I resumed the study of senile alopecia, in the hope of perhaps finding here these degenerations particularly well developed, without flattering myself that I would discover any causal connection between senility and alopecia. The length of the hairs on the cheeks of old men, where the skin is certainly always much degenerated, is often very remarkable. But to my astonishment, there were very few degenerated fibres in the alopecia scalp. Only now and again did I find a few fibres of elacin. In an old woman of eighty, I found no elacin in the bald scalp, while the skin of her face was filled with degenerated elastic fibres.

It must therefore be reserved for the future to discover sharp distinctions between Alopecia senilis and the last stage of Alopecia seborrhoica; as yet we have none, and I can therefore only point to Alopecia seborrhoica for the more exact description of the conditions which I found in the bald heads of old people.

What is said of Alopecia senilis is true, in perhaps greater degree, of Alopecia præmatura. The single important difference, in my experience, is that, in premature alopecia, the seborrhœic symptoms are sometimes concealed. They are never completely absent; they are either for the time being slight, or have previously been greater; and, further, the character of the falling out of the hair —in opposition to Alopecia neurotica and Alopecia areata—exactly corresponds to that of Alopecia seborrhoica. Here also we must look to future investigations for a useful differential diagnosis.

Alopecia Neurotica.

There is no longer any doubt that in certain streak-formed alopecias, limited to nerve regions, or appearing after traumata, neuralgia and other nervous affections, we have true neurotic alopecia, while typical Alopecia areata is more and more certainly a contagious affection. While the latter form has often been histologically examined, we have no positive histological criteria for the neurotic form; neither the fallen-out hair nor the affected skin has been examined.* Schütz believed

* In the streaked alopecia, following traumata and neuralgia, I have never found the "point of exclamation" hairs of Alopecia areata.

that he could determine from several such cases, where the streak-formed spots developed into triangular baldnesses, with the apex towards the occipital angle, that the hairs fell out in bundles, corresponding to the natural direction of the hairs, from the definite points of convergence.

Trichorrhexis Simplex.

The simple splitting of the hair from the apex more or less down into the shaft, is always the result of external, inappropriate treatment. It is found in all neglected long hairs, both in the beard and in the head. It is particularly frequent in the beard, which is exposed to many injuries, among which frequent greasing stands first.

As far as the fissures reach, the cuticle externally, and the medullary substance inside, disappear over large areas. The brush-shaped points consist only of rind substance, and it is remarkable what length these thin horny prisms may reach, without any tendency to break. The brush-like distribution after loss of the connecting cuticula, is a result of the concentric pressure which the rind substance of the hair undergoes from the muscular hair follicle and the proliferating prickle layer of the hair follicle over the papillary apices. But the tendency to break down into long, very independent horny prisms appears to me to be combined with another peculiarity of many hairs, which was first recognised by Flemming and then by Giovannini, but which is by no means rare, namely the multiplicity or at least the many plied form of the papillæ belonging to individual hairs. Especially the thick hairs of the moustache and whiskers show, on cross section, now and again, a division of the papilla, which either reaches right down to the base, or only to the upper end of a common papilla, a sort of ridge system dividing it into two, three, and even four divisions. The cortical substance of such double, triple, or quadruple hairs runs together, and is kept in connection by a common cuticle and root sheath, but the cross section of the hair shows, in the under part of the follicle, according to the number of the papillary apices, a very small elliptical or clover leaf form, which only in the upper part of the follicle becomes more rounded. Such hair shafts must retain a tendency to spread in all directions, even outside the follicle, and when the cuticle is lost, readily fall asunder into separate long points. It is owing to this that the brush-like hairs, in typical cases of splitting of the beard hairs, are found, on section, strikingly elliptical, or with three or four angles. Only, of course, an increased division does not of itself explain the phenomenon of simple trichorrhexis ; the end of the hair must either have been torn or have lost its cuticle.

Following this form of true trichorrhexis come the inconstant, irregularly formed tears, which are limited to short areas of the hair shaft, mostly at the points, but which also occur in the shafts, as a result of a lesion of the cuticle, and in which there is no abnormally increased tension of the rind substance, as in the cases just described. These, therefore, have less interest. We group them together as Scissura pilorum.

Trichorrhexis nodosa, Broom hairs.

This change in form of the hairs, which was well named Trichorrhexis nodosa, is regarded by some authors (Michelson, Kohn) only as a symptom, not as an independent disease. It is quite admitted that in several diseases of the hair (Alopecia areata, traumatic injuries of the cuticle), a splitting of the hair takes place after previous vesicular distension of the shaft. But I cannot regard those cases as true Trichorrhexis nodosa, which is distinguished by the fact that, without any pathological changes and with proper attention to the hair, greyish-white nodules appear, at pretty regular intervals, in the hairs of the beard (more rarely on the pubis, axillæ, and very rarely on the scalp), in which the shaft may be bent and torn, and a previously existent, punctiform, very marked transverse bulging distends both ends like a broom. Since the same conditions appear in the traumatic nodular rupture (rupture of the cuticula and transverse bulging), as in Scissura pilorum, these forms of rupture are now and again combined. But in the true disease, Trichorrhexis nodosa, there must be added, as in Trichorrhexis simplex, some special mechanical factor, which, in spite of the absence of ordinary injuries, and in more widespread and obstinate manner, leads to much more marked changes in form.

As the first indication of the later nodules, we find, as the first investigator, Beigel, recognised, spindle-shaped distensions of the medullary substance, which compress the rind, distend it, and give origin to tears of the cuticula. In the complete nodule, sometimes double the size of the hair shaft, the distension of the cortex has gone so far, that it gives the impression of two brushes or brooms stuck into each other (Beigel). The cuticula at these places is hardly more recognisable than the medullary substance; the latter disappears a little above and below the nodule, showing that it is not any change extending from the papilla into the medulla, which causes the splitting of the shaft. Beigel and Kohn recognised that, on the addition of nitric acid and caustic potash, not only more air than usual escaped from the diseased parts, but that apparently unaltered regions of the shaft were distended; these reagents therefore demonstrate the first stages of the disease. Beigel concluded from this, that a spontaneous development of gas in the medulla was the cause of Trichorrhexis nodosa; a theory which has not been maintained by any other author. Kaposi and Schwimmer regard peculiarities of the hair development as the cause, while Wolffberg seeks it solely in external injuries. Kohn

believes that the affection commences with drying up of the medulla, which permits the entrance of air. Naturally this could only replace the water (see Leucotrichia), and could not distend the cortex.

Another of the earlier describers of the affection, Wilks, assumed that we were dealing with a fungus affection of the hair, and, as a fact, the punctiform distension of the shaft, completely independent of the root, would be easily explained by the penetration of gas-forming germs. But these have not yet been recognised. All later investigators have had it in view, but their results are all negative. The black and the blue masses, as well as the few and inconstant spores, are all recognised as accidental impurities. I too have sought in vain for fungi in ordinary Trichorrhexis barbæ. But, of course, with the incompleteness of our methods for the recognition of parasites, this negative result is proof of nothing. Dr Menachem Hodara from Constantinople was recently successful in my laboratory, in cultivating a well-characterised bacillus, which appeared to be the cause of an affection closely allied to our Trichorrhexis nodosa barbæ. According to Dr Hodara, a form of Trichorrhexis nodosa is very common in ladies in Constantinople, and these were the hairs he examined. This Trichorrhexis nodosa capillitii of women leads to miniature nodules similarly constituted to the large ones we know of the beard. After the culture of a peculiar bacillus, Dr Hodara found it, microscopically, inside all the nodules, and finally he was able successfully to infect, with a pure culture of the bacillus, the hair of a female. There were seen on her previously quite normal hair, even with the naked eye, the nodules of the Constantinople affection. As I conclude this chapter, Dr Hodara is busy with the further question, whether this bacillus is found in Trichorrhexis nodosa, and is able to produce it, and whether the two affections are identical.

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Monilethrix, Spindle hairs.

This change, which was first described by Walter Smith, consists in a series of thinnings of the hair shaft, which thus looks like a string of beads. Since, at the thicker intervals, the ordinary colour of the hair appears, the hairs usually have a piebald aspect, but must not be confused with the ringed hairs of Leucotrichia annularis. At the thicker intervals the hair is normal. The length

of a spindle is about 1 millimetre, about one day's growth. The affection has several times been found in families, and has often been noted in early childhood; though it is not present at birth, it is possibly congenital in origin.

Smith and all after-investigators determined that the thinned parts of the hair are the diseased parts. The intensity of the thinning varies very much; sometimes the appearances are not evident macroscopically, and are just indicated microscopically. We see definitely, that the hair shaft, where there are no constrictions, is quite normal or at most somewhat broader (Behrend, Bonnet), but it shows no formation of nodules. The old expression (nodose hair) is therefore not very appropriate. Where on the hairs the constrictions are just indicated, we see at the same time three things: a thinning of the medulla, a thickening of the cuticula, and an internal displacement of the cortex; so that the thinned central medullary column tends sometimes to one, sometimes to the other side, and consequently the thickness of the cortex varies on different sides of the medullary canal. Properly, this appearance is to be regarded otherwise, namely as a spiral twisting of the whole cortex around a central axis. All these symptoms are present, in lesser development and irregularly distributed, even in normal hairs: both the thinning of the medullary canal and its eccentric position, and the simultaneous thickening of the cuticle. But only its prominence, and the intermittence of the symptom, characterise the first stage of "spindle hair." But these three facts indicate, where they occur, a hair production taking place under great external pressure, in which the factors of growth-pressure, acting from the papilla radially outwards, are restrained by the pressure of the follicle membrane and the prickle layer of the follicle, acting radially inwards.

These symptoms are still more clearly seen where the constrictions are greater, and especially where the spindles proper are produced. At these areas of maximal constriction, the medullary canal is completely absent, and the cuticula is thickened to about twice its original size, by the coalescence of the cells. Excess of lateral pressure has completely obliterated the central medullary production, and has pushed closer together the normally-formed cuticular cells. The displacement of the cortical cells holds an intermediate position, the internal ones, like the medullary cells, undergoing complete removal, the outer ones, like the adjacent cuticular cells, being only restrained—this, at least, is the simplest explanation of the very varying thickness of the whole cortex, at the areas of constriction. At the finest constrictions of the hair—in comparison with the unconstricted parts—a large part of the cortex must, like the medulla, be impeded in its advance.

While the description of these deformities of the hair shaft is clear enough, we learn from them little of the nature of the resistance which

the hair shaft experiences. For, *a priori*, we may just as well have an intermittent aplasia of the germinal layer of the medulla (Behrend), as a relative increase of the centripetal pressure in the hair follicle, and the latter may depend just as well on an excessive contraction of the follicle muscles, as on a too abundant production of the prickle layer.* Only histological investigation *in situ* can decide this.

The only observation which we possess is that of J. A. Scott, who examined one of Wallace Beatty's cases. In every follicle which produced monilethrix hairs, there were found at least two spindles; but many follicles contained also normal hairs. In the affected hairs, the follicle and prickle layers were normal; all were, as was to be expected, papillary hairs. Henle's layer of the root sheath, and the cuticle were normal. The cuticula of the hair could be seen, as a layer of oblique cells, only at the constrictions, not between them. The only alteration was in Huxley's layer of the root sheath, which, corresponding to the renewal of the hair, was everywhere much thickened. This striking difference between Henle's and Huxley's layers of the root sheath, of which only the latter filled up the constrictions of the hair by a corresponding thickening, Scott and Beatty rightly attributed to the fact, that Henle's layer cornifies early, and only Huxley's remains soft and vigorous in the larger part of the hair follicle. The authors found the distribution of pigment the same, both in the constrictions and in the normal intervals,† and they therefore attributed the darker colour to the greater thickness of the former.

Thus the restraining cause of the restricted growth of the hair would exist in a periodic swelling of the still protoplasmic parts of the root sheath, either consisting in a periodically increased proliferation, or an oscillating compression of the elements of the root sheath. The third possibility, of a pathological swelling of the root sheath cells, cannot be considered, for while it would allow the sudden constriction, it would not the immediately following distension. The intermittent formation permits only two possibilities: an oscillation of proliferation of the epithelia, or the same of the muscle tone. This the authors do not discuss, and a further investigation of the mitosis of the root sheath, and of the elastic and muscular elements in the under part of the follicle, is necessary.

I must now admit that with my view of the active powers in this central part of the hair follicle, only the second possibility can

* We can only assume periodical, intermittent and disappearing conditions. It is not possible to attribute the constrictions to persistent pathological swellings of the root sheath or of the hair follicles.

† Unfortunately the authors always speak of "nodes" and "inter-nodes," although they themselves recognised, both clinically and histologically, that no nodules existed.

be seriously considered, and I consequently regard the thickening of Huxley's layer, which Scott found, as an appearance of stagnation, completely parallel to that of the hair cuticula (and of the external cortical cells). Only we knew nothing previously of this thickening, for the elements of the root sheath break off at the escape from the hair follicle. It is to me incomprehensible how a simply increased proliferation of the matrix of the root sheath should not only be arrested in regularly alternating periods, but at the same time, by multiplication of its elements, could undertake the still more difficult task of hindering the advance of the central elements of the hair, while what one would expect is that the root sheath would only advance more rapidly or more slowly along the hair. But an increase of the contraction of the follicle perfectly explains all the appearances of monilethrix, and to it I will presently recur.

This mechanical explanation of hair deformity has been supported by a work of Bonnet on hair spirals and hair spindles. This investigator found in the autumn casting of a horse's coat, spirally twisted and often spindled hairs, enclosed in the hair follicle. Bonnet attributes these spindles to the fact, that the plastic young hair masses are pent up before the isthmus, which is produced underneath the sebaceous gland region by an unusually powerful development of the circular musculature of the follicle. The advancing mass is constricted like a spindle by the contractile follicle, as the pressure in the hair mass diminishes, while a new collection underneath the isthmus causes the penetration of a second spindle. We see that the intermittent spindle formation is not due to an intermittent force, but only to an increase of the normal elastic or muscular contraction of the hair follicle in its central region; a hypothesis which leaves nothing to be wished for in simplicity, and further has the advantage that it can be proved histologically.

Bonnet's description corresponds with the case of Luce, where the hair spindles from the bald head of a child were also retained in the follicle.

Finally, I will reiterate the histological factors which favour this *mechanical theory of the development of spindle hairs*: the thickening of Huxley's layer of the root sheath (Scott) and the penning of the cuticular cells of the hair at the constrictions, the thinning and spiral winding of the medulla, the twisting of the cortex in the same direction, and lastly, the approximately equal size of the spindles; this latter, only because this theory assumes the antagonism of forces of constant strength. On the other hand, the complete absence of the medulla and the differences in the degree of constriction, by no means contradict this mechanical theory.

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Transient and periodical greying of the hair.

Leucotrichia, Ringed hair.

The persistent greying of the hair, *canities*, will be described under the pigmentary atrophies. Here we have to consider those changes of colour in the hairs which are induced by an increased amount of air in them, and are analogous to the *Flores unguium* and *Leuconychia* (see the next chapter). Accounts of a sudden change in the colour of the hair, from dark brown or black to grey, have roused suspicion as to the credibility of these statements, since the dependence of the colour of the hair on pigment was familiar. In these criticisms we have over-looked the fact that the hair colour depends largely on the porosity of the hair, and that a hair which contains much air, and on transmitted light is dark, may appear white by reflected light. In recent literature, completely trustworthy statements as to this occurrence have increased, so that the possibility of a sudden greying is now established. The question only is, whether such a condition indicates a persistent greying or only a transient change of colour, and if this goes on to persistent greying, in what way it does so.

It is important to note, that the colour of the hair in older people undergoes periodical changes in this direction. Severe and prolonged nervous irritation, loss of sleep, and mental work, have especially a marked influence, not only on the moisture and greasiness of the hair, but also on the whole epidermis. The hair becomes dry, stiff, rough, and of a lighter shade. Repeated disturbances of this sort may, in a short time, cause the whole hair to appear greyer than, to judge from the amount of pigment, it should appear. But in such cases, there is usually very soon added true greying, with loss of pigment, and it appears as if the same nervous influences which induced the transient

dryness, also favoured the persistent loss of pigment, so that the idea of acuteness appears to be confirmed. In some carefully observed cases of transient nervous disturbances, the complete restitution of this transient paling has been observed.

> Reinhard observed in a female idiot, a periodic change of acuteness and stupor, each period lasting about a week, with a transitory period of two or three days. Sometimes there was also a variation of the cutaneous temperature and secretion. The hairs, which in the active periods were dark golden-red, became, during stupor, yellowish, rough and dry. The change in the hair advanced from the apex towards the root, and corresponded to a microscopically visible multiplication and enlargement of the spaces in the hair. Käuber observed in an epileptic, periodically recurring changes (loss of shining, roughness, felting, alteration of the dark blonde colour into foxy red, scissura pilorum, trichorrhexis), which appeared suddenly in the hair of the head ; and further, widespread angio-neurotic disturbances of the scalp, and alopecia. Paget saw, in a lady who suffered from periodic headaches, some parts of the hair become white after each attack. In a delirious patient, who became grey in a night, Landois could recognise the cause in a dense permeation of the hair with air bubbles.

In all the cases yet known, the porosity of the hair is altered in its whole length. The normal air spaces are all enlarged, although the oldest, upper parts of the shaft are more exposed to drying than those near the skin. But there are also cases of periodic increase of air, in the sense that some stretches of the shaft show a dense permeation with air, while those parts lying between, remain quite normal. The former are then usually completely refractile, and quite white, although they have the same amount of pigment as the rest. There develope in this way, piebald, and, if there is periodicity, *ringed hairs.*

I have once met with this condition in a case of Leuconychia, and have described it under the name, Leucotrichia. The blonde, scantily and equally pigmented hairs were, in the white stretches, coarsely porous in the cortex, and closely beset with spindle-shaped air bubbles. Where a medullary canal existed, it was no longer visible inside these air-containing stretches. But the circumscribed porosity was quite independent of the medullary canal and its air. The cortex showed, in the normal segments, a moderate number of air bubbles, mainly in the central parts, so that the hair shaft showed, towards the periphery, a denser horny substance. The cuticula was everywhere well preserved, and usually somewhat broader than normal ; there was never any distension or constriction to be noted on the hairs.

A similar but more regular development of the air-containing segments was seen in Karsch's well-known case of *ringed hair* (Leucotrichia annularis). Spiess and Landois showed that the white rings

were caused by a complete filling of these areas with air bubbles. The collection of air was independent of the medullary canal, although it extended in its direction. In this case, there were intermittent swellings of the surroundings of the hair; partly, but not exactly, the thickenings fitted into the air-containing spaces, but there were no constrictions present, as in spindle hairs. Since Karsch has used the name "ringed hairs" (pili annulati) for this affection, it is advisable not to use it occasionally for the spindle hairs (monilethrix); at most, one may call the true banded hairs, analogous to those of animals, ringed hairs (see canities), for there at least we have the patchy change in colour. The development of air segments, I explain in the same way as in leuconychia, as a periodically increased softness of the cortex, by which the segments in the hair follicle become more succulent, while those outside become drier, and absorb air.

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Atrophy of the Nails.

The sudden falling-off of the nail-plate or a large part of it, is, in almost all cases, the result of a solution of the physiological connection between nail-plate and nail-bed. This is, of course, not organic, for the horny ridges of the nail-plate are only inserted between the ridges of the nail-bed epithelium, and are therefore only fitted in. This mechanical connection may be acutely or sub-acutely dissolved by a change of the nail-bed alone, usually an increase in size. But it is not conceivable that there can be any such sudden solution in the region of the nail matrix, where the nail-plate has an organic connection with the underlying epithelium, and is united to the mother epithelium by a very well-marked prickle and fibrillary apparatus. Every surgeon knows that he may push a blunt, flat instrument with comparative ease under the nail-plate, as far as the lunula, where the advance of the instrument is absolutely arrested; and that the nail-plate, which has been readily separated from the nail-bed, cannot here be separated from its root, but only after division, can be laterally removed in halves. And we find also, that, generally, the most recent part of the nail-plate, which covers the nail matrix, remains adherent in acute shedding of the nail, and the portion which covers the nail-bed rather tends to break off in smaller or larger masses, than to bring the root portion with it.

Total loss of the nail most readily results from very severe bruises and other traumata, which, affecting the nail fold alone, induce marked ecchymosis over the whole surface of the matrix, and lead to breaking up of the matrix epithelium. But usually, bleeding only takes place from the wide veins of the nail-bed underneath the nail-bed epithelium. Thus the ridges of the nail-bed are suddenly elevated and widened, and there takes place, between them and the ridges of the under surface of the nail-plate, a displacement, which loosens their connections. On the nail, which is now elevated from its bed, all sorts of external mechanical forces act, and soon lead to its breaking and falling off. Now and again, the blood appears directly under the nail-plate, and extends, like the scissors of the surgeon, between it and the nail-bed epithelium.

In many nervous disturbances, subungual hæmorrhage plays (as the experience of Joffroy and Pouget shows), a considerable rôle, without the occurrence of any traumata. These authors have, in cerebral paralysis, multiple sclerosis, and especially in tabes, examined cases in which a subungual bleeding always preceded the sudden casting of the big-toe nail, which was regularly repeated at intervals. This was preceded by paræsthesia, formication, deafness, and pain on pressure, which suddenly ceased with the appearance of bleeding. Pouget notes particularly, that these paræsthesiæ are not to be compared with the lightning pains, or the neuralgic crises of tabetics, which, from Strauss's observations, may also be succeeded by cutaneous bleedings. This author therefore believes that the bleedings must not be ascribed to a neuralgic, but to a vasomotor disturbance, of which it is questionable whether it causes, or only accompanies the casting of the nail. The casting of the big-toe nail is in these cases always symmetrical, but not usually simultaneous on both feet, and may be repeated oftener on one foot than on the other. In the process, the nail-bed, apparently healthy, lies as if dissected ; there is never inflammation or ulceration, and the nail is rapidly replaced.

It must be left undecided, whether in these cases of tabes, &c., hæmorrhage always induces the casting, and is its cause ; it is possible that it is often overlooked. But if, as Pouget states, a similar acute casting occur in these nervous diseases without hæmorrhage, we must regard the latter only as a favouring factor, and not as the ultimate cause, which is always, in my experience, an expansion of the ridge system of the nail-bed. This is well known as a late symptom of syphilis. The anterior part of the nail, often of several, and sometimes even of all the fingers and toes, becomes decolourised, yellow and opaque, and ultimately (when split from the nail-bed, and air has got under it) chalky white. In the painless casting of this part, which usually comprises half or two-thirds of the whole nail-plate, we see the thickened longitudinal ridges of the nail-bed lying before us. There is no inflammation or hæmorrhage ; the thickening of the ridges of the

nail-bed—here evidently a specific affection of the latter—is the one cause of acute casting of the nail-plate.

Constitutional disturbances, such as syphilis and diabetes, are not essential to the production of this phenomenon. In old people, shedding of the nails sometimes occurs without any apparent cause, though usually it is confined to a broad portion of the big-toe nail. This is due to senile changes in the whole configuration of the toe. The nail-plate is bent somewhat backwards, the horny layer of the nail-bed ridges is very much thickened, and the nail-bed is somewhat shortened. These latter changes are evidently the primary cause of the loosening of the nail-plate, and the whole proceeding appears to me as if there were a modified onychogryphosis commencing, in which, from the commencement, nail-plate and nail-bed are less accurately fitted into one another, and therefore separate from each other, instead of the thickened horny layer of the nail-bed and the nail-plate—as usual—rising together.

In these latter, not infrequent cases, the casting is less acute ; the discolouration of the nail prepares the way, and the solution is sometimes not quite complete. The nail-plate is thrown off in a very chronic and irregular manner in cases of purulent perionychia, both staphylogenic and specific, which latter, especially in hereditary syphilis, sometimes affects all the finger nails. Onychia maligna, in which the new, growing nails are constantly undermined and broken off, comes under this category. While in the former cases the nail is simply thrown off like a dead horny mass, by the underlying suppuration (analogous to the horny covering of an impetigo vesicle), in this latter affection, we are possibly dealing with an infectious inflammation of the nail itself.

These last-mentioned changes of the nail, form the transition to a large class of very interesting, but as yet only little histologically investigated onychoses, which we may combine under the name : *changes in the consistence of the nail plate.*

Here we have certain secondary changes of the nail substance, the results of the perionychial suppuration just referred to. Here, frequently, if the suppuration has lasted long, part of the adjacent matrix is attacked, and then produces the soft, cloudy, lumpy, opaque nail mass, which, seated like a wedge in the otherwise healthy nail, gradually dries up, and leaves a depression or an actual hole in the nail-plate, which gradually travels forwards. The surrounding parts of the nail are then saturated by serum and pus, and transformed into a sort of crust, which on drying becomes dark brown and horny.

These partial degenerations of the nail-plate produce white spots on the nail, the so-called *flores unguium.* In the majority of cases, they

are produced by their owners causing numerous small injuries of the matrix, in pushing back the fold of skin with a pointed instrument. Unlike the forms of leuconychia, to be immediately described, they are quite irregularly distributed. Their development is by no means clear, and it would undoubtedly advance our knowledge of cornification if investigations could be carried out on animals. Probably it is the same process as occurs spontaneously in the different forms of leuconychia *i.e.*, collections of air in the nails, which appear at the seat of areas of softening. They might then be described as *Leuconychia traumatica vel punctata.*

> Morison described a *Leuconychia striata* in a lady of twenty, who had noted for some months, perfectly white, cross marks on the finger nails, which appeared at the lunula and advanced with the nail. They disappeared in summer, and reappeared in winter.

Morison found the cause of the white colour, in air bubbles, which were chiefly seated in the central layer of the nail, and, corresponding to the layers, were oblique from behind forwards. This indicates a focus of disease affecting the larger and central part of the matrix, in which an epithelial softening takes place intermittently. The simultaneously softened epithelial collections must then be arranged in an oblique central nail layer, and, as they dry up and air enters, lead to the development of white cross furrows.

> An analogous process, though much more extensive, is that of *Leuconychia totalis*, described by Giovannini and myself. In my case, which lasted from childhood, all the nails were opaque, and so soft that they did not need to be cut; they simply exfoliated at the border. Their colour was, posteriorly, bluish white, anteriorly, chalky white; in front the nails were somewhat bent, and air had evidently entered and converted the bluish-white colour into a chalky white. While the posterior portion, which embraced a good deal more than the lunula, was white all over, and showed on pressure no change of colour, the chalky white colour in front consisted of white transverse bands, which were separated by fine, reddish-brown ones. These were connected by brownish longitudinal lines, and disappeared on pressure, when blood was seen through the again transparent nail substance. The chalky white bands disappeared gradually, posteriorly, into a few white points. The surface of the nail was smooth. The nails of the feet were normal. Some of the blonde hairs of the young man were affected with Leucotrichia (*q.v.*).

In the clippings from these cases, the air bubbles, in contrast to Morison's case, are found mainly in the upper and under part of the nail, while the somewhat firmer central core only shows finer air bubbles. The lowest layer of the nail-plate usually shows large, longitudinal protuberances, which, on cross section, produce a festooned contour of the nail-plate, and correspond to the thickened ridges of

the nail-bed. The softer consistence and less resistance of the nail-plate, lead on the anterior part of the nail-bed, to the formation of a subungual horny layer, which favours the bending of the anterior nail-border, the drying of the nail-plate, and the entrance of air into the latter. In Giovannini's case, the drying and the entrance of air appear to have developed only at the anterior border, and the nails were not so soft.

The main point in the process is not the entrance of air—that is a secondary phenomenon—but the abnormal softness, and a certain condition of swelling of the nail cells, by which they become opaque, and the nail-plate, as a whole, bluish. From the point where the nail-plate lies free, the nail cells suddenly dry up, and the nail-plate becomes transparent, unless the entrance of air induce complete refraction, and a chalky colour by reflected light. This secondary appearance is found, in specially soft nails, at first in points, and later, in the centre of the nail bed, in streaks and bands.

Allied to leuconychia is a by no means rare condition of the nails, which, on account of a certain superficial resemblance, is usually considered as eczema of the nails. But it differs from eczema, and shows itself to be a pure disease of the nails, by appearing simultaneously on all the finger-nails, and sometimes on all the toe-nails also, while the skin surrounding the nail is healthy, and there is no eczema elsewhere. I could not find any constitutional causes, at least there were none constantly present.

The affection heals invariably, though slowly, under arsenic. The nails are, from behind forwards, thickened, inelastic, hard, rough, opaque, and have a yellowish-grey colour. The lunula is no longer marked. There often appear longitudinal furrows, while in other cases the whole surface is covered with protuberances and depressions, and the anterior border is rough and irregular. There is no diminution in consistence, and no tendency to exfoliation or to tears of the border, such as occur in eczema of the nail-plate. The affection may last unchanged for years, and produces a very unpleasant appearance of the hands.

This condition of the nail-plate, which, to distinguish it from eczema of the nails, I call Scleronychia, is not based, like Leuconychia, on an abnormal softness of the nail cells; on the contrary, these appear to be of normal, or even abnormal hardness. The slighter transparency depends not on large air bubbles, although I found the normal small air bubbles increased. There must be some unknown specific change in the nail cells, and some specific affection of the nail matrix. The nail-bed is perfectly healthy, and does not share in the process. Possibly, Scleronychia is only a manifestation of a general anomaly of cornification of the body, which only on the nails has reached such a degree as to be evident, and thus is only recognised there.

The opposite condition to Scleronychia is found, in some individuals, in a peculiar want of coherence in the nail cells, which is shown in splitting of the free border. The nails, otherwise, are of normal appearance, smooth, shining, and not discoloured. Only in the neighbourhood of the tears are they opaque, grey, or yellowish. But these places do not correspond with definite areas of softening in the matrix. They do not extend forwards with the nail-plate, but, on the contrary, extend from the free border backwards ; they are the results of external injuries on the abnormally unresistant nail substance.

Of this anomaly also, we have no histological investigation which might explain its peculiarities. It cannot be of the nature of softening, such as occurs in Leuconychia, for the nail substance retains its transparency until it splits. Possibly, more recent anatomical experience in this question leads us to the right explanation, that in all these surface epithelia we have to distinguish a homogeneous protoplasmic substance, from a system of epithelial fibres which run through their protoplasm. One may conjecture a softening of the homogeneous protoplasm and atrophy of the epithelial fibrillation, and it is possible that the former exists in the different forms of Leuconychia, the latter in that absence of cohesion which is shown in Schizonychia (tendency to splitting of the nail-plate). This could be determined with proper methods of investigation on nail clippings.

These different, complicated, regressive changes are succeeded by a whole series of simple atrophies of the nail, which indicate the persistent or transient casting of a larger or smaller part of the nail substance. Here arises the question, whether a simple arrest of nail production must cause evident microscopical change in the configuration of the nail. The fact, that at those times in which mitosis of the whole epidermis is arrested, *e.g.*, in febrile diseases, typhoid or pneumonia, no visible signs of an arrest in epidermic growth are visible, does not justify us in assuming this of the nail. For the luxuriant epithelial growth on limited places, such as here, makes the nail a much better test for slight variations in epidermic growth than any other part of the body, even the hair. It has long been noted, that the nails, in certain general disturbances of the lunula, in frost-bite, cholera, and fractures of the bones (Duplay), for a time cease their growth. If growth begin again, the old nail is usually separated from the new by a distinct furrow, and is often different in colour, the young undergrowth being more distinct and less yellow than the old portion of nail. More accurate investigations are those of Vogel on that partial atrophy of the nail which invariably accompanies certain febrile diseases, especially typhoid, typhus, measles, and pneumonia. Vogel draws attention to the semiological and forensic significance of white streaks, furrows and swellings of the nails, which have already

been noted by Reil and Beau, and whose presence points definitely to the previous existence of one of these, or some similar febrile disease.

> The commonest is, according to Vogel, a white "anæmic" streak, two to three millimetres broad, which is not quite white, but very much the colour of the lunula, so that it can first be distinguished from this when it is a little advanced on the nail bed. In contrast to Leuconychia punctata, it always forms a complete transverse band, and is not sharply limited like that. But even where this white band is only indicated, the directly following nail zone has a remarkably irregular surface. Where the transient arrest of the nail is greater, there appears, along with the other symptoms, a partial atrophy ; and there is formed a transverse furrow, which is deepest in the centre, less so at the sides of the nail. Usually, the anterior edge of the furrow is abrupt, corresponding to the actual febrile commencement of the disease, while posteriorly it is more gradual. It is very important to note that, at the furrow, not only the thickness, but also the breadth of the nail diminishes, so that the longitudinal ridges of the nail come closer together on the furrow. In many nails, but especially in that of the thumb, the furrow is margined anteriorly by a transverse swelling, which also occupies the whole breadth of the nail, and in some cases is the only thing present. The streaks, furrows and swellings always appear symmetrically, and from them we can always fix the date of the disease.

Vogel's observations, since they have not been confirmed by histological facts, and vary much among themselves, offer great difficulties of explanation. Generally speaking, in those phenomena which point to a disturbance of the function of the matrix, there are two possibilities of development, which I may shortly distinguish as "vasomotor" and "trophic." According to the vasomotor theory, we are dealing with differences in the amount of blood and lymph in the tissue around the matrix, especially of the base and cover of the fold. The better these are supplied with blood, and the more the natural turgidity is increased, the greater will be the pressure exerted on the nail which forms in the fold ; it becomes thinner, and is more rapidly advanced. If the congestion of the fever is gone, the nail becomes thicker, and is once more slowly formed. This vasomotor theory explains the sudden diminution of the nail thickness, *i.e.*, not only the furrow, but perhaps also the formation of the white stripe, and the absence of burnish on the subsequent nail substance. But it would be difficult to explain the primary thickening and the transverse swelling of the nail in this way.

In contrast to the vasomotor theory, which ignores trophic disturbances, and considers only the mechanical results of abundant lymph, the trophic theory simply assumes an arrest of mitotic formation, conformable to the general view, that in febrile diseases, in which there is great consumption of tissue, mitosis is very soon arrested. This theory would explain the transverse furrow, for in diminished advance of the nail cells, the normal tissue pressure at once narrows the nail fissure, and the new formed after-growth appears as a more contracted plate.

The swelling seems difficult to explain by this theory, but if we follow the changes more carefully, we see that it can be done. As I have already pointed out, the separation of the nail cells in oblique layers, from behind forwards, leads to the fact that a partial diminution of growth at the posterior papillary end of the matrix results in a depression, while at the anterior a-papillary end of the matrix, it is followed by restoration of the plane. The one leads to thinning, the other to thickening of the nail, which grows more slowly in both cases. The paradox, that the same absence of nail-substance produces in most cases a furrow, but frequently also a swelling, and almost always a slight thickening before the furrow, is explained by the varying amount of atrophy of the elements of the nail matrix, the basis of which lies in the varied development of the papillary body inside the nail-bed. A simple furrow would consequently indicate more marked diminution of growth at the posterior papillary part of the matrix, a simple swelling, the same at the anterior part, while in the mixed cases, the stoppage of additions to the nail varies from before backwards, in a wavy manner, over the nail matrix.

The white stripes and the dulness of the surface are, however, not so fully explained by a purely trophic theory, and, so far as I can see, we must assume a combination, *i.e.*, tropho-vasomotor. I mean this of course not in the sense that congestion can produce mitosis; this old view has got its quietus, and moreover would here be of no value, since we have to do with an arrest in mitosis; but in the sense that the congestion of fever may act more on the partially atrophic nail-fold, by lateral pressure, than on the normal, and that on the other hand, the matrix, which uses less material for mitosis, and is therefore better nourished, will give origin to more juicy nail cells, *i.e.*, to a white band and a duller surface.

And I must not omit to note, that the deformities of the nail-plate (cross furrows, and cross swellings) not only accompany atrophic processes, but are frequently added to inflammatory changes of the nail (eczema, syphilis), where their occurrence is, of course, more easily explained.

I have described as stagnatory nails, a special form of partial atrophy of the nail, which developes in adults who suffer from various forms of disturbed circulation.

I have found this remarkable form in emphysema with general cyanosis, in those suffering from cold hands and feet, chronic constipation, hæmorrhoids, bleeding from the kidneys, but most marked in the general stagnation of the limbs in a leper. It exists in these cases for years, with relapses, but may also disappear. There are formed circumscribed, longitudinal swellings of the nail-bed, especially in the central part, over which lies the nail-plate, thrown into

angles, but otherwise intact. These angles are much higher than the ordinary longitudinal marks. The cohesion of the nail-plate suffers at these places, and it breaks off at the anterior free border. Then reddish, soft swellings appear in place of the sharp angles, thinning the nail-plate over them, and not permitting it to meet in the centre, so that, instead of a uniform nail-plate, there exist two lateral wings. The separated parts often cross each other in front, especially on the thumb, and thus the resemblance to folded wings is still greater. If the reddish, longitudinal swelling begins before the lunula, it is regular and small, *i.e.*, it represents a few very much thickened ridges of the nail. But in some cases the formation of the swelling extends into the lunula, and then it expands posteriorly, occupies the whole breadth of the lunula, and, the nail-plate in the centre completely atrophying, gradually unites with the covering of the nail-fold. Then the skin of the back of the finger passes directly into the central swelling, and the whole nail formation is limited to two small wings, coming from the lateral angles of the matrix.

Although we have no anatomical investigation, it is clear from the whole course of the affection, that we are dealing here with a simple pressure-atrophy, from swelling, especially of the central nail-bed, on the basis of venous stagnation. The long direction of the swelling indicates that the stagnation is superficial, and in the papillary body of the nail. Thus, as the process extends backwards, the papular elevation extends laterally, corresponding to the lateral extension of the superficial vascular net of the lunula, while the superficial capillary loops of the nail-bed are arranged in the same direction as the folds, and can therefore only lead to longitudinal swelling. This limitation of the longitudinal swelling to the most superficial part of the nail-bed, is especially evident in the rare cases in which the symptoms of deeper stagnation are added to those described. Then we have a deep transverse swelling of the whole nail-bed, which causes the longitudinal swellings and the remains of the nail to take the form of a gentle wavy bending; but this does not alter the character of the longitudinal swellings. For, on the places where the nail angles break off, and at the height of the swelling, no hypertrophic horny layer of the nail-bed is visible; the elevation of the nail-bed owes its existence entirely to the stagnation in the cutis. From the gryphotic process, the stagnatory atrophy of the nail is totally different, as it is from that atrophy of the nail accompanying the atrophy of the finger-pulp, which we shall consider directly.

In contrast to partial and transient atrophies of the nail, complete persistent ones are rare. This is the best place to distinguish atrophies of the nail-plate from those of the nail-bed.

Apart from the changes due to accidental traumata, and limited to the nail matrix, we find *a total atrophy of the nail-plate* only in those cases where the whole nail-fold is obliterated by some affection which leads to scars (Panaritium, Pustular syphilide, Variola). If only a

small remnant of the base of the fold persist, a small, stumpy nail grows from this pocket. In such cases, the epithelium of the free-lying nail-bed always proliferates, and produces an irregular, supplementary nail, which gradually diminishes by shrinking of the nail-bed, and never forms a true nail-plate. The conditions are quite different if the atrophy first attack the nail-bed, and after this is completely gone, passes secondarily to the nail-plate. Here we have to explain the rather remarkable fact that the same factors which we have seen led to gryphosis in onychogryphosis, *i.e.*, atrophy of the pulp of the toe caused by the pressure of the boot, and the general atrophy of the skin of the ungual phalanx, may as easily lead here to an atrophy of the nail, commencing with the nail-bed. Only this condition is much rarer than that. If the pressure meet the nail in otherwise healthy tissue, it leads to in-folding and gradual shrinking and swelling of the nail-bed, with their ultimate result: gryphosis. But if the same pressure causes a general stunting of the ungual phalanx, the nail-bed atrophies (the pulp of the toe advancing on to the surface of the toe), shortening the nail-bed down to the nail-fold, and leading to displacement and diminution of the nail-plate.

I have examined the toes of an old woman, which showed this form of nail atrophy in its full development. The pulp of all the toes is diminished, and reaches, since no proper nail-bed exists, to the thin nail-plate, which arises perpendicularly and almost naked from a flat nail-fold.

Longitudinal sections through the ungual phalanx, show a marked atrophy of the bone, which, towards the point, is directed upwards more than normal, and has lost touch with the nail-bed lying above it. The pointed end of the posterior nail-fold lies, relatively to the bony phalanx, in its normal position, somewhat above and in front of the posterior articular condyle. From here, the pocket containing the rudimentary nail arises abruptly upwards. The posterior side of it corresponds to the previous covering of the posterior fold, and is, apart from its abrupt direction, not importantly altered. Its epithelium is, as usual, in three layers, and extends into the epidermis of the pretty much unaltered back of the toe. The anterior side of the vertical nail pocket corresponded to the matrix, the whole nail-bed, and a not inconsiderable part of the finger-pulp, and is therefore, since it cannot ascend higher than the posterior side of the pocket, reduced to a fourth or sixth of its normal size. This shortening affects the individual elements very irregularly. The matrix is somewhat, but not very much shortened, the nail-bed, however, is pressed into a comparatively small segment, shorter even than the matrix. This upper third is formed by the triple epithelium of the toe pulp, which reaches with a remarkably

thick horny layer into the nail-pocket, and aids in pressing the escaping nail backwards. In relation to their structure, these three segments have undergone no important change. The epithelium of the nail-bed consists of a prickle layer arranged in ridges, which, without producing a horny layer, permits the advance along it of the nail-plate. A few a-typical epithelial processes and horny pearls in it can hardly be regarded as pathological. The cornification of the epithelium of the matrix into nail cells proceeds normally; we can easily demonstrate remains of nuclei in the latter, and, even in regard to its staining power, the nail-plate appears normal, and certainly does not resemble the keratomatous condition of onychogryphosis. Thus the change of the epithelial elements is limited to the marked shortening of the nail-bed, and the elevation of the nail. The shortening is not accompanied by a swelling of the nail-bed, as in Onychogryphosis, but is a pure atrophy.

The connective tissue surroundings of the nail are of course also affected. With the atrophic bony phalanx, the finger pulp is displaced outwards, and forms a blunt cone, which is somewhat directed upwards. The epidermis, the coil glands, and their fatty tissue are normal, except for displacement of their elements. But in front of the nail-pocket, the cutaneous tissue thickens remarkably, a distinct result of the pressure which has pushed the nail-bed backwards, and shortened it. The collagenous bundles are here thickened, lie close together, and are arranged parallel to the nail-pocket; they are permeated by abnormally numerous spindle-shaped connective tissue cells. This fibromatous change of the cutis in front of the nail-pocket affects nearly double its breadth.

This description corresponds to a stage of atrophy, in which the nail-plate, except for its displacement, has undergone no change. But other nails show that it is gradually affected. The nails are first thinned, then the nail-pocket is also shortened, and, finally, may be completely atrophied, this, of course, leading to the permanent loss of the nail.

If we examine the toe-nails of those persons who show gryphotic changes on the big toe, we find, now and again, especially on the small toes, instead of gryphosis, this form of atrophy of the nail-bed, without growth of the nail-bed epithelium, and with more abrupt elevation of the nail-plate. The processes are very closely allied etiologically, and it depends on circumstances, whether onychogryphosis or total atrophy of the nail-bed developes. Under these circumstances, general atrophy of the skin, and nervous trophic disturbances, play the main rôle in general atrophy of the nails.

Here we shall shortly consider those changes of the nails which have been described by Weir-Mitchell, after wounds of the nerves,

and which are related to other cutaneous disturbances, of regressive character, such as splitting, thickening, and stunting of the nails. Most of them are comprehensible as the mechanical results of atrophic changes in the cutis. A total arrest of growth does not occur after division of nerves, indeed, nails thrown off may be replaced; but, according to Weir-Mitchell, the growth of the nail is slower—an observation which could not be confirmed by Vulpian and Bernhardt. In cerebral paralysis, in which, according to Weir-Mitchell, growth should be completely arrested, Bernhardt found, in certain conditions, even more active growth. So much at least we learn from these recent investigations, that nail growth is pretty independent of nervous influences. In future, researches must be undertaken with more caution. It is not sufficient, as has previously been done, to measure the growth by marks on the surface of the nail, for a slower advance of the mark may occur without slowing of the growth, if there be simultaneous thickening of the nail-plate. We must always bear in mind the deformities of the nail, which are in direct dependence on the trophic changes of the nail surroundings, and thus, in general nervous disturbances, are rather to be expected than direct influences on the nail growth through the nerve centres. The same caution must be observed in that thinning of the nail generally regarded as atrophy, which one now and again meets in people who have been long in bed, and in cases of bone disease, scrophula, and rickets. Here also, the thinning of the nail is not always a sign of atrophy, but often enough only of deformity, and the result of an accompanying deformity of the finger and toe ends. In all such cases the observation of marks on the surface of the nail should only be considered along with weighing of the clippings, to get at the true facts. The same remark is true of the accidental and very varying deformities of the nail from traumatic changes of form of the nail-fold, into which we cannot enter. Here, also, the diagnosis of an atrophy of the nail should not be made, without weighing the nail parings.

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Atrophy of pigment.

In the diminution of pigment in the skin, the great question which concerns us in the accumulation of pigment—the iron question—is of less importance. For here we are dealing, generally, with long-standing pigmentations, whose origin from the blood, even if recognisable, is an event long past. We have therefore here to do only with melanoses, and are face to face with the often asked, much discussed, but still unsolved question: how does the pigment disappear? Since the migration of pigment has been recognised as beyond dispute, the possibilities have much increased. We know definitely, that the actinic melanoses, Ephilides as well as the general browning of the exposed parts of the skin, gradually disappear under cover, or on avoidance of light, and also—and this is the simplest case—that depigmentation is due to diminished chemical attraction of pigment to the surface of the skin. But, since chemotaxis may be negative as well as positive, it is not impossible, that, under certain circumstances, the pigment may be directed from the surface downwards by similar but opposing influences; that, according to Riehl and Jarisch, a backward transport to the cutis from the epidermis may take place. *Vitiligo* especially has impressed itself on various observers as an inward attraction of pigment. But I can only admit a backward transport, if it shall be proved, that the pigment lying in the cutis has exactly the same properties as epithelial pigment, which is, notoriously, in general, darker and more finely granular, and, according to Schmidt, older than the cutaneous pigment. I must say that I have never seen cutaneous pigment which seemed to me to have been for a time in the epidermis, though I have not myself had the opportunity of examining Vitiligo skin. The backward transport of epithelial pigment to the cutis is consequently as possible as it is questionable.

Beyond doubt, on the contrary, is the disappearance of pigment, by a destruction which it undergoes in and by the epithelium. Aeby and Karg regard pigment, though only in the form of pigmented leucocytes, as a form of nourishment of the epithelia. But that pigment regularly disappears in the epithelium, is shown in all faintly pigmented parts of the epidermis, *e.g.*, in normal European skin. The pigment never reaches beyond the lowest layers, and as it advances outwards, becomes more scanty and faintly granular. There is no possible reason why pigment should not, like other firm bodies which get into the epithelial lymphatics, be scattered over the whole prickle layer, and reach up to the granular layer, unless it disappear in contact with the epithelium. The only question is whether it is transformed into a colourless mass,

or entirely perishes, whether it is assimilated by the epithelium and serves for its nutrition, or whether it is dissolved and returns into the lymph stream. Abnormal consumption of pigment is the only explanation of certain appearances. Such are the disappearance of pigment on deeply browned areas of skin (genitals), under the influence of inflammation accompanied by epithelial growth—for example in the fungating syphilides and acuminate condylomata, and in the change of negro skin to white, described by Morison, under the influence of Syphilis and Psoriasis. The consumption of pigment remains, in each individual case, a hypothesis, until the behaviour of the pigment granules is followed in detail, and found to agree with the hypothesis.

Ehrmann has put forward a new explanation of the disappearance of pigment. According to him, requisite for pigmentation are certain pigment-containing cells, whose origin is obscure, but which, on account of their invariable connection with epithelium, are very probably of epithelial origin, and of which we only know that they are supposed to represent, in human skin, the chromatophores of the amphibia. Ehrmann believes he has proved that these cells are absent when the disappearance of pigment sets in. But whether their absence may not as well be the result as the cause of the absent pigmentation, has not yet been sufficiently thoroughly investigated. I have not yet been able to satisfy myself of the existence of cells which have the peculiarities of pigment carriers, and can therefore not very well ascribe the disappearance of pigment to the absence of such cells.

Blaschko takes a wider view of the question, and rightly notes that on the broad way from the blood to the epidermis, the most varied obstacles may oppose the transport of pigment. Now, since the pigment is often arrested at the epithelial border, the suggestion is quite a good one, that here, normally, there is some obstacle to the transport, though it may not be the absence of Ehrmann's "porters." But this resistance cannot, as some think, be due to an absent capacity for taking up pigment, in the individual epithelial cells, for the simple reason, that we know of no disappearance of pigment in which the pigment reaches to the borders of the individual epithelia. For then it must lie in the lymphatics of the epidermis, and the skin would be dark. But the pigment must, in disappearance of pigment, accumulate, if anywhere, *under* the border of the epithelium.

Consequently, of the various hypotheses, the following three are probable, and to be kept in mind in the future study of histological details: *consumption of pigment by the epithelium, backward transport from the epithelium*, and *stagnation under the epithelium.*

We have placed together the scanty literature on the two affections which come mainly into consideration: *Vitiligo* and *Canities.* The

reticular pigmented syphilis, which is often classed with them, belongs, as has been shown elsewhere, to another category.

Vitiligo.

Vitiligo is an acquired, circumscribed or general depigmentation, which appears in the form of round, symmetrical spots, which, when discrete, simply enlarge, when unlimited, run together, and with the advance of the disease, may lead to widespread polycyclical surfaces, and to the total loss of cutaneous pigment. The hairs on the affected part are also decolourised. The depigmentation is always preceded by a slight, diffuse hyper-pigmentation ; when this usually unnoticed first stage is more persistent, the hyper-pigmentation around the pigmented area is so distinct, that it appears as if all the pigment from the white spot had collected here. We therefore sometimes see mentioned a "displacement of pigment," although there is no proof of any lateral displacement. In the vitiligo spots of the hairy regions, this dark brown halo is absent, for here the primary pigmentation of the epidermis is not so distinct. The partially depigmented cutaneous areas show a concave, nibbled margin, like a normal collateral net, although, of course, much more irregular. The causes are unknown ; sometimes Vitiligo succeeds to a locally limited depigmentation from scars or areas of pressure, or to an acute exanthem, or some other infectious disease. Under its influence, congenital pigmented moles may be depigmented.

G. Simon noted, that in Vitiligo, the pigment in the prickle layer was absent at the white spots, and in the surroundings was present in normal fashion ; otherwise the skin appeared healthy. Caspary, who in his work on pigment especially endeavoured to find pigmented spider cells at the epithelial border, did not find them on the border of a vitiligo spot, while the basal epithelia contained pigment in the normal way, but more abundantly.

Further facts we owe to Wermann, who confirmed the disappearance of pigment in the epidermis at the neighbourhood of the white spot, but drew attention to the fact, that it was present in the cutis, though less in the centre of the spot than at the borders. But the cutis at the brown marginal zone is much more deeply pigmented ; here, particularly the papillary body, but also the surroundings of the vessels, follicles and glands, show numerous oval and stellate, branched pigmented cells. Some lie on the epithelium, but Wermann could no more than Caspary, recognise a penetration of the processes of the connective tissue cells into the epithelium. In the epithelium of the dark border, the pigment is dark brown to black, and is both inter- and intra-epithelial. In the cutaneous cells, it has the golden yellow or brown colour of blood pigment, but never gives the iron reaction. In his preparations, he found very many mast-cells in ordinary distribution, and among them some which contained pigment granules as well as mast-cell granules. Wermann suspected, like Bogoliubsky,

Karg and A. Philippson, a genetic connection between mast-cells and pigment cells, which in general is certainly not present.

The absence of pigment in the vitiligo spot is explained, on the ground of the recognition of pigment in the corium, by Ehrmann, according to his theory, by absence of ascent of the pigment, by Jarisch, according to his theory, and agreeing with Riehl, as a descent of the pigment; but neither of these views is supported by thorough histological details.

From all this, we only see, that in Vitiligo we are dealing with a pure and primary affection of the pigment; all the difficulties of the pigment question are here present together.

Canities.

Canities embraces only that greying which developes in old people —and exceptionally in young ones—by loss of the hair pigment. The pigment in the hair, as in all epidermic structures, is known to be present in two forms. One lies and remains between the epithelia, as dark brown, finely granular, melanotic pigment, and in cornification of the hair cells, and their advance, is simply taken with them as so-called granular pigment. The other one is taken up by the lower germinal cells, assimilated, and colours them from a light to a dark brown. This pigmentation does not always withstand cornification. There is a consumption, perhaps only an oxidation of pigment, inside the hair cells, so that these, as they rise inside the hair follicle, become light. In all dark, brown and black hairs, the hair cells take with them in their substance a good deal of this, as so-called diffuse pigment.

In general, the amount of intra-epithelial diffuse pigment is in proportion to the abundance of inter-epithelial granular pigment, but there are also hairs with faint, more diffuse or more abundant granular pigmentation. But abundant diffuse pigmentation is never found along with feebly granular pigmentation, a circumstance which is very much against an autochthonic development of the pigment in the hair cells. To this melanotic pigment is added the light yellow colour of horny substance, which every dry albuminoid substance shows.

This last, of course, does not disappear in senile greying, but it is over-compensated by the amount of air in the hair, so that the latter, if it contain no melanotic pigment, usually appears actually "silver white." Which form of the pigment usually disappears first in senile greying, is not yet determined. It seems to me that the diffuse pigment disappears first, for one often finds white hairs with quite unpigmented cells, and scattered collections of granular pigment.

Nor are we certain how the decolouration takes place. It is in general assumed that the formation of pigment simply ceases at the papillary border, and that a white hair at once forms, which pushes on the dark one and gradually replaces it. But this is easier to assume than to prove. For, as a healthy hair daily grows about 1 millimetre, we would see on every single hair, in men for one or two months, and in women for years, the appearance of piebald, white and dark banded hairs, before complete whiteness ensued, and this no one has observed. Indeed, it is most difficult to find anywhere, hairs which have their roots white and their apices still dark. The only author who has carefully investigated this point is Pincus, who admits that, exceptionally, the point first becomes white; and Michelson in v. Ziemssen's text-book, simply adopts this statement, although—taken without reservations—it indicates a depigmentation of the entire hair, such as was believed in at the beginning of the century.

Some explanation of such exceptions, we find in observations such as those of Pincus, Richelot and Falkenheim, according to whom a *transient* true greying takes place from absence of pigment.

> Richelot observed in a girl of seventeen, so long as she suffered from chlorosis, most of the brown hairs becoming white for about two inches from the root; then came a brown after-growth, which pushed the white band before it. Falkenheim found in a man of thirty-three, whose head was grey, alternating light and dark bands, in which the amount of hair was the same, and only the amount of pigment different. Pincus also found such banded hairs in canities.

Of course, in such cases one might meet with white points with dark roots, but these cases are not only extremely rare, but we see at once that ordinary greying cannot take place in this way, or these piebald hairs would not be so remarkable.

Another explanation would be that the pigmentation gradually diminished from the root, and thus the margin between white and dark pieces could not be distinct. We would then meet, on a greying head, hairs of all stages, up to complete whiteness. This explanation will hardly suffice. We know that Brown-Séquard found, on his own beard, and to his own astonishment, that the white hairs became suddenly white over night, and often in their entire length. He epilated all the white ones, and found that, in addition to many which were only bleached at their root, there were always some freshly bleached, perfectly white ones. I believe that anyone who pulls out every white hair as soon as it appears, will have the opportunity of confirming these observations of Brown-Séquard, though they are not compatible with the ordinary view of a simple pushing forwards of the dark hair by the growth of the white ones. This must be verified anew, by careful investigations.

We know no more of the histological proceedings than of the anatomical. Ehrmann alone has given us a somewhat summary statement, which I will repeat almost verbatim, for otherwise I fear that the not very comprehensible view of the author will suffer. In the hair papillæ, in the hair bulbs and between them, there are found branching, anastomosing, pigment-containing cells, which convey the pigment from the cutis to the hair. "These appear to be combined with similar cells of the hair itself, which however, the further up they are, have the fewer processes, and finally pass into the cells of the substantia propria of the hair. But while pigment cells are always present in the papilla, even in quite white hair—the only exception is senile atrophy, where these cells also perish—we miss the pigment preparing cells, in certain conditions in the hair bulb. The hair may then become white, in spite of the production of pigment in the corium, for the colouring material, though produced, does not reach the hair, because the bearers are awanting." This view certainly demands attention. But it will be noted that Ehrmann says simply it *may* be so. He does not give one single observation as to the histological behaviour of the different papillæ and hair bulbs of the scalp where the hair is greying, from which one might draw conclusions as to the genesis of the process. His proofs are merely investigations on the hair in premature juvenile canities, in which the cells described are absent in the bulb, and it is evident that Ehrmann does not wish to apply his theory of the *absence of pigment carriers* as the basis of greying, to the ordinary senile canities, for he distinctly says, that in senile atrophy even the papillæ of the hair contain no pigment. It therefore only causes confusion, and it has led to much misunderstanding, when Ehrmann says later: "If one examines white hairs (?) he will find, if the soil is otherwise healthy (?), distinctly pigmented cells in the hair papilla, but none in the bulb."

We have then a theory on the histogenesis of premature greying (and vitiligo of the hair of the scalp), but none of senile greying: what we require are facts. The theory of Ehrmann in relation to premature greying "in otherwise healthy soil," has the weak side, that his "pigment carriers," which are neither leucocytes, ordinary connective tissue cells, nor simple epithelia, are very difficult to distinguish, in the upper layers of the hair bulb, from the hair cells which are found there. Further investigation is required to clear up and simplify this matter.

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2. After previous Hypertrophy or Inflammation.

Scars.

By scars, in the proper sense of the word, I understand only that tissue which is newly formed locally, after some defect of the cutaneous tissue, and has certain peculiarities which distinguish it from the normal cutis. It is by no means proved, though usually held, that the new formation *must* be distinguished, macroscopically and microscopically, from the cutaneous tissue. As it was previously believed that suppuration was necessary for healing and granulation, it is still generally believed that normal cutaneous tissue cannot be reproduced. But it may now be concluded, from the possibility of certain therapeutical effects on scarring, that we may again reach complete accord between new formed and old cutis;* in other words, a second intention without scar formation. The peculiarities which distinguish the scar are—(1) absence of epidermic marking, that is, smoothness of the horny layer; (2) anæmia; (3) thinning of the corium; (4) loss of normal elasticity; and (5) more or less complete loss of follicles and coils, and the associated fatty tissue and secretion. A series of atrophies of the skin, which appear, not as replacing defects, but as the last stage of inflammatory processes (Ulerythema), and are often regarded as scarring changes of the skin, have no more to do with these than other atrophies of the skin.

The scar developes from granulation tissue, which we have considered under the progressive disturbances of nutrition of the cutis. As soon as this has reached about the level of the surrounding vascular cushion, the granulation flattens down, sinks in, and is covered from the side by young epithelium. Before the epithelial border developes, the rest of the base of the ulcer is exactly like that of old granulation tissue. We find in it the vertical vessels narrowed into isolated cords, and between them, in columns, the collagenous plates alternating with plate cells, which, only towards the surface, give place to a looser young granulation tissue, with fibrillæ and spindle cells.

At the side, underneath the young epithelial border, the horizontally-arranged firm tissue of the plates is more developed, and there, where the surface is cornifying, approaches the young epithelium, without actually reaching it. There is always a sub-epithelial streak, without that condensation of the collagenous tissue which distinguishes the old granulations. This transparent sub-epithelial streak appears, with a low power, as if a new papillary body had been formed, while

* That is cutis in the narrower sense, without the enclosed organs.

it only indicates the border of the advancing condensation of the tissue. The scarring ulcer is thus surrounded by a broad shell of old granulation tissue, which, beneath and laterally, passes gradually into the normal cutaneous tissue. This transition, which is of course very important in distinguishing the cutis from the scar tissue, usually takes place thus: — the flat structure of the collagenous tissue disappears, and with it the flat form of the enclosed connective tissue cells. The collagenous tissue then becomes still more condensed, and it is almost impossible to make out any structure; it becomes almost a homogeneous substance, with numerous spaces. In this lie the cells, of which one can see little but the nucleus. With a good protoplasm stain, we see, however, that they are, as before, surrounded by a remnant of protoplasm. There is certainly here an increase of the collagenous substance, at the expense of the spongioplasm of the fibroblasts. This external condensed shell of old granulation tissue shows, with polychromic methyl-blue, special preference for the methyl-violet, which it retains with most methods of decolourisation, while the younger granulations and the normal cutis always give up this colour readily. The further transition into the cutis tissue takes place somewhat suddenly, the firm collagenous mass being loosened into first unarranged, and then arranged fibrillary bundles, and the methyl-violet mixed with the ordinary tinges. At the same time, the greater portion of the cells disappears altogether, and the adjacent cutis contains very few more spindle cells than normal.

The condensation of the collagenous tissue, from beneath and from the sides, towards the centre of the ulcer, corresponds to a change in the subcutaneous vessels, which may be described as endarteritis and endophlebitis obliterans. The lumen of the largest vessels underneath the scar is distinctly narrowed by ridges in the arteries, and by concentrically-arranged, reticular plates in the veins. This obliteration gradually extends to the vertical capillaries, of which one always finds some with an irregularly narrowed lumen, and others converted into obliterated cords. With this increase of the collagen outside and inside the capillaries, and the disappearance of the cells around them, the elastin which is often formed in older granulations around these vessels, also disappears. The granulation, before it is converted into scar tissue, becomes completely free from elastin, with the exception of a few deeply browned clumps, the irregularly scattered remains of the old elastin.

During this period the epithelium of the surroundings has expanded over the granulations, in the form of a gradually advancing border, and thus the prickle and horny layers are usually not a little thickened. Of the different layers, the prickle layer extends furthest towards the

centre, and at first dries up on the surface, without forming a horny layer. On this innermost ring, follows a second one, in which the prickle layer is thickened, sends ridges into the granulations, and is cornified on the surface. But this cornification is far from regular. The horny layer, which may be much thicker than normal, is formed without the interposition of a granular layer; it corresponds to the horny layer of the mucous membrane of the mouth, and this part of the border is therefore red and transparent. Outside this, comes the third zone of the advancing epithelium, bluish white and opaque, in which true epidermic cornification, with the formation of kerato-hyalin, takes place.

It is of great importance, that this young epithelial border freely sends epithelial ridges downwards, when it meets normal granulations. Nor is this remarkable, for the granulations, as we have seen, are formed in columns, and between the vascular columns is an inter-vascular tissue, which certainly presents less resistance than the upper ends of the blood vessels. Therefore, in epithelial new formation, the vessel's loops are preserved, new papillæ are formed, and a new ridge system sinks down. In general, it reaches as far as the upper layer of the granulation, consequently forming a papillary body of abnormal dimensions, which sometimes reaches an astonishing size.

It is consequently only a legend, which appears, however, to be widespread, that a scar is formed wherever the papillary body is destroyed, "because it cannot be re-formed." This view is quite untenable, in view of Auspitz's observations. For if the papillæ were fœtal and constantly furrowed from the cutis, pathologically, they could certainly develope from soft granulation tissue. And that the papillary body is more easily depressed by mechanical changes of pressure on the surface than completely destroyed, is shown repeatedly in these pages.

But after complete destruction of the papillary body, along with a great part of the cutis, there developes a much larger papillary body than previously present, and if many later scars only show a few papillæ and ridges, or none at all, this must be due to some peculiar *secondary flattening of the papillary body*, characteristic of the scarring process.

Of thirty-two scars which I have examined in this connection, and which mostly come from the leg (after ulcers, ecthyma pustules, eczema, tertiary syphilides) I only found eight which showed none or very much stunted papillæ. These were very smooth, sunken, some white, some deeply pigmented scars, whose considerable age could be concluded partly from the altered character of the collagen, and partly from the commencing new formation of elastin. In ten scars there was a

feebly-developed papillary body present; in the other fourteen, papillæ were present in numbers, and varied much in form and size over the whole extent of the scar. Only in a few cases did the ridge system diminish in height and thickness towards the centre. The papillary body and ridge system were particularly well developed in several old scars, in which the skin around showed eczematous or other chronic changes; and in three quite young scars, which represented just cornified granulations. On the a-papillary scars, the upper layers of the cutis always consisted of a particularly loose and relatively a-vascular connective tissue, exactly comparable to the horizontal plate of the papillary body in normal skin. As we do not speak of a disappearance or a destruction of the papillary body, in other dermatoses where this vascular, loose connective tissue layer exists between the firm cutis and the epidermis, but indicate the change only as a stretching and flattening of the papillary body and ridge system, to a level surface, so in scars, the expression, disappearance or absence of the papillary body, should not be used where only the papillæ are absent. In this upper cutaneous layer of the scar, and—as in view of the frequency of papillæ we may rightly say—in this *papillary body of the scar*, we find the most important differences between individual scars.

One often finds, limited to this region, on staining the sections with polychromic methyl-blue, a reddish colour of the collagenous substance, similar to that which is got on staining the mucinous umbilical cord. There also appear here, or on other scars in the papillary body, numerous mast cells, which often have their methyl-red granules widely distributed. Some scars are distinguished by the great dilatation of a few sub-papillary veins, which clinically are superficially evident. In other scars again, we find here a good deal of golden yellow or reddish brown blood pigment, the remains of previous hæmorrhage in the granulations. But the pigment is not limited to this most active region of the scar. Of the thirty-two scars which I have examined, eleven contained a considerable amount of pigment. In two, the pigment formed a complete net all through the scar, reaching from the scanty subcutaneous tissue up to the epidermis, and pigmenting the two lower rows of the prickle cells. In other cases, it followed only some capillary vessels. But the scar is, in general, by no means so deficient in pigment as is usually stated. Karg's investigations show that the originally white scar of negro skin is gradually completely blackened by immigrated pigment. I also had the opportunity of examining a scar from a negro's skin, which was completely black, and was only distinguished from the tissues around, by the smoothness of the surface, and the want of epidermic marking, it being thrown into coarse folds, parallel to its long direction. Here

there was a new, very irregular papillary body over the whole scar, and the ridge system was distinctly thicker and higher than that of the normal surroundings.

It is most interesting to observe, that even the dark brown melanotic pigment was more abundant in the scar epithelium, than in the epithelium of the healthy skin, and that the adjacent papillary body only contained the pigment in amount, at the seat of the scar. Evidently the power of attraction of the young epidermis of the scar for the melanotic pigment, which must be considerable in negroes, ultimately leads to excess.

The coarse marking of the scar, parallel to its long direction, is often found, and is evidently to be attributed to the contraction of the scarring cutis. The same process also induces, in most cases, the softness and succulence of the papillary body, the dilatation of its vessels, and the limited but distinct mobility over the scar, which we can often clinically determine. So long as this force continues, there cannot, of course, be a regeneration of the cutis tissue from the scar. But after passive movement, to which every scar is exposed, the nature of the collagenous tissue often alters. The coarse, sclerotic collagen assumes once more a normal fibrillation, which commences in certain bundles, and gradually extends all over the scar. At the same time its reaction to basic colours disappears. But these adhere better to the protoplasm of the cells, the spindle cells increase in size, the blood capillaries in extension, and, finally, new elastic tissue is developed. The appearance of this latter is so peculiar, that it cannot possibly be confused with persistent remnants of old elastin, apart from the fact that this, after so long a time, has usually disappeared, or is only found in fragments at the periphery of the scar. With a good orcein stain, we see, running parallel to the horizontal collagenous substance, pretty broad elastin fibres which, on section, show a rounded or oval form. Cross cut bundles therefore look like drops. But it seems to me that the elastic substance in these places appears at once in the form of threads, which do not show the windings and net formation of normal elastin. They are, in general, broader, and stain somewhat less, and with a good stain, a clear central cylinder is noticeable. But I would not conclude from this, that young elastin has a tube form. I have as yet observed the development of new elastin only in four old scars, but I regard the possibility of it as very important, in connection with the reorganisation of the scar.

If we inquire what changes must occur that true cutaneous tissue may take the place of the scar, the following is the answer. In the first place, the secondary disappearance of the papillary body and the ridge system of the epidermis must be avoided. Since both are present

in excess in young scars, and the resultant normal contraction of the scar tissue in the depths of the skin very much favours the preservation of this superficial excess of tissue, the reasons why in many scars it more or less disappears, must be sought elsewhere. These I have found, on the one hand, in the too extensive formation of true scar collagen, and of those above described firm collagenous plates, which too soon arrest the formation of the papillary body, and cause contraction of the surface of the skin; and, on the other hand, in a too marked vascular obliteration, by which the nutrition of the papillary body must greatly suffer. Since the conditions for the formation of a new papillary body are present, it is only necessary to secure the elevation of the firm collagenous substance, which we can do by mechanical (massage) or chemical (salicylic acid, resorcin) agents, and to keep the scar vascular, which also is within our power.

Secondly, one must endeavour to abbreviate the normally very slow replacement of granulation tissue by new cutis tissue, and as far as possible to avoid the intermediate formation of those coarse, contractile plates. Here also, in the treatment of young scars with the above-named remedies, we are able to interfere in the scarring process, and if attention is directed to it, we will find numerous better methods.

The definite thickness of the scar is also at our discretion, as soon as we can exclude the secondary atrophy, for we have learned the period of cornification of the granulations, as well as to command completely the growth of the latter.

Finally, the spontaneous new formation of elastin guarantees the elasticity of the reorganised scar.

After this review of the development of scar tissue, there only remains the consideration of some interesting points, which have previously not had much attention, I mean the relation of the coil glands and the blood pigment to the scar, and the appearance of a particular sort of connecting substance, namely, elacin.

By their deep position, the coil glands frequently escape the ulceration which precedes the scar, while the follicles usually suffer. We therefore find, deep down in many scars, well preserved coils. In these there are, almost invariably, changes to be recognised, first, in the circumspiral and interspiral connective tissue, which is swollen, homogeneous, and sometimes of the same structure and staining power as scar collagen, even if the surroundings show loose fibrillary tissue. The coils are always larger than normal, from swelling of their epithelia and lumen, and the loops of the coils are often closely pressed together. Finally, we find in many scars an irregular proliferation of the epithelium, which leads to the projection of humpy protuberances, and to partial closure of the lumen—the foundations of

adenoma formation, which are found in greater degree in stagnatory fibromatosis, and in the surroundings of varix.

The pigment of scars, if it be present in excess (I exclude negro's skin), always succeeds to thrombosis of the endophlebitic or varicose veins of the hypoderm, and has a special interest, because in such cases we are undoubtedly dealing with blood pigment, which may with certainty be followed up to the epithelium of the surface. It is interesting to note, that it always gives in the cutis the iron reaction (with HCl and K_4FeCy_6), while at the same time, the somewhat browner granules of the epithelium no longer give it. Further, some granules in the cutis, especially those which are still small and very light golden yellow, do not give the reaction. We are therefore dealing with a *transitory* iron reaction of the blood pigment of scars, a fact which very well corresponds with the observations of Schmidt on the iron reaction of blood pigment.

Finally, in four scars I was able to determine the presence of elacin, sometimes with, sometimes without the new formation of elastin. We have, in these cases (as described in erysipelas, and with better staining methods, in the senile skin), the slightly wavy, sharply round, undivided, smooth, refractile fibres and fibrillary bundles, whose resemblance to elastic fibres is undeniable, but which, in distinction to these, take the basic stain (methyl-blue, safranin), from an alkaline solution. We find them here also accompanying regressive processes of the skin, and as a product which does not undergo destruction, but with appropriate staining, appears as a sharply margined, solid, persistent structure. In one case, the scar throughout its whole thickness contained a net of elacin.

Ulerythema centrifugum.

(Erythème centrifuge, Biett; Lupus erythematosus, Cazenave.)

Peppercorn to lentil sized, bluish-red, flat papules, whose centre is somewhat depressed, and either covered with dry, yellowish scales, or smooth. They appear usually multiple on the nose, cheeks, ears, and hairy scalp, more rarely on other parts of the body, and gradually extend, the elevated border advancing, and the depressed centre enlarging and then slowly atrophying. By confluence, large areas may be affected at once or successively. Very rarely there are universal outbreaks with fever, like an acute exanthem, which, with the addition of pneumonia and other complications, often end fatally; in these cases, the papules are converted into large, brownish-red nodes (Kaposi). On the fingers, the eruptions resemble ordinary small chilblains, which are covered with a central adherent callosity.

Characteristic of the primary eruption is the appearance of comedo-like horny plugs, which only partly correspond to the mouths of the follicles on the elevated border, the occurrence of similar plugs on the under side of the central

scale, and the formation of comedo-like horny cysts on places where strong hair grows (scalp, eyebrows). Characteristic of the scar-like atrophy, which appears spontaneously, is its superficiality and softness, as well as the absence of keloid-like swellings, and enclosed, isolated papules. The occurrence on the palms and on the mucous membrane of the mouth shows that the affection is not necessarily connected with the mouths of the follicles. In rare cases, the eruptions appear as if seated on spastic, œdematous white papules (Ulerythema centrifugum papulatum), so that there is a resemblance to Urticaria and Erythema multiforme.

Considering the great number of able works, the histology of the disease should, at least in its main elements, be established. Particulars of the initial inflammation and swelling, and of the ultimate atrophy of all the constituents of the skin, we have galore. But a characteristic general view, which shall reflect the clinical peculiarity of the affection, we seek in vain.

To the two clinical forms of scaly, and smooth, simply depressed papules, there correspond two forms of epithelial change. Either the affection begins at once with a hyperkeratosis, which, since a corresponding epithelial growth is absent, leads to a flattening, a shallow, dimpled depression of the surface. This form is found mainly on the hairy scalp, where the surface epithelium in this disease hardly shares in the growth; but it may appear elsewhere—on the ears, the neck, forehead, etc.—wherever the acanthosis in individual cases remains absent. Or—and this is the most frequent form—along with excessive cornification we have a marked epithelial growth, which does not, as is so often assumed, remain limited to the mouths of the follicles, but leads on many places to a marked increase in width and length of the epithelial ridges. Especially in the centre do these widened ridges sometimes run together to a thicker epithelial swelling, which depresses the cutis in the centre, flattens out the papillary body, and stretches the elastic net into parallel cords. But this acanthosis never leads to a projection of finger and toe processes into the cutis, as may occur in Lupus. The proliferating prickle layer is rather again flattened into a few layers, in that a cellular growth of the cutis opposes that of the surface, and the epithelium as it grows downwards also undergoes deeper cornification. In typical cases of this nature, which are clinically distinguished by a thick scale, and whose seat of predilection is the centre of the face and the back of the hand, the papule is, in the centre, covered by a homogeneous, horny callosity, one millimetre or more thick, whose basis is below the level of the marginal parts, and which extends in a series of round, short, conical, horny plugs. Where the primary acanthosis is most marked, these horny plugs only rarely correspond to the follicular entrances, but to some other proliferated areas (Miethke), most frequently to the centre of widened epithelial ridges. Where,

however, epithelial growth of the whole surface is slight or absent, we often find the externally visible horny plugs to be connected with the mouths of the hair follicles. Even where no horny plugs dilate the mouths of the follicles, these are plugged by thickened horny layer from the surface, and where strong hairs occur in the follicles, as on the scalp, the eyebrows and the beard, the constant production of hair produces cystic dilatations of the plugged hair follicles, which are filled with cast-off hairs, horny lamellæ, and fat. These hair cysts, which are rare and small in the lanugo hairs, are responsible for all the references to milium and the like. They have nothing to do with the previously noted solid horny taps of the surface, which are always enclosed by a broad granular layer; and in future no one should speak of them as milium-like bodies. True milium does not occur in Ulerythema centrifugum.

While dealing with the epithelium it is well to give precisely our view as to the rôle of the follicles and the sebaceous glands, on which much that is contradictory and superfluous has been written. Hebra senior, solely from the clinical view, and on account of the plugs on the under side of the scales apparently coming from the sebaceous glands, stated that the sebaceous glands were the point of origin of the affection. Consequently, the earliest histological workers (Geddings, Neumann, Kaposi), sought and found changes in these glands, and Kaposi, in addition, in the sweat glands. Geber was the first to recognise that all the glandular affections were secondary and complicating, and to note the point of origin in the papillary cell growth. Since then, the rôle of the sebaceous glands in the affection has gone up and down, but all previous investigators are inclined to attribute to them, changes, which are sometimes noticeable and then do not exist, or are slight and then usually incorrectly explained. Thus almost all observers state that the glands appear "hypertrophic," without noticing that the apparent hypertrophy occurs on the skin of the face, where the enormous development of the sebaceous glands is physiological, and that the regions of the smaller sebaceous glands, *e.g.*, the scalp, show no hypertrophy, nor any signs of hypertrophy, formation of new lobules by epithelial growth, etc. Further, many investigators speak of hyper-secretion, and they base this view on the occurrence, which really almost excludes hyper-secretion, of the stagnation of fat in the plugged follicles. The description of destruction of the sebaceous glands by masses of granulation, or by wandering cells, must also be attributed to the incorrect explanation of lateral sections of the gland. The single true change which is everywhere evident on the large sebaceous glands (Schütz) is the complete fatty change of all the glandular cells, right down to the fundus of the gland; an occurrence which is present in all

stagnations with closure of the follicle, and is only a proof of commencing glandular atrophy. Indeed, many of the facts, which, in a desire to support the sebaceous gland theory, have been brought forward, and have by constant repetition acquired a certain appearance of verisimilitude, are absolutely incorrect. All the sebaceous glands undergo simple atrophy, the more rapidly, the greater the epithelial growth of the surface. Beneath the proliferated central ridges on parts of the face, where there are small follicles and no hypertrophic sebaceous glands, we see very well how the upper part of the hair follicle passes into the acanthosis of the surface, and of the sebaceous glands only a few fat cells remain. Where the epithelial growth of the surface is absent, and the follicles are simply plugged by horny masses, the small sebaceous glands either remain unchanged, or gradually atrophy, for there is no after-growth of young epithelium. The same is the case in most of the hair follicles with strong hairs, especially where hair cysts are formed. Thus the sebaceous glands only persist, where they have already, physiologically, reached an abnormal size; the secretion stagnates in them, and dilates the duct, which sometimes becomes spiral. The glandular cells all become fatty, and if the fat stagnates above, the atrophy may remain at this stage without showing any further changes. But if the fat can reach the surface, even the large glands atrophy, although this very common occurrence is not of any importance in the pathogenesis of the disease. At the height of the process, the majority of the small sebaceous glands has almost disappeared.

As we see, the follicles as a whole, play a purely passive rôle; only the region of the infundibulum shares in the ultimate epidermic growth, the central and lower regions remaining normal and producing hairs, which may collect in superficial hair cysts. This limitation is explained by the initial, usually superficial seat of the inflammation. From what has been said, the origin of the affection must be sought neither in the follicles nor in the sebaceous glands; often enough they are, as Geber noted, quite normal, amidst marked inflammation of the surroundings. It is high time to get rid definitely of this sebaceous gland theory, for it is founded on insufficient clinical observation. The horny plugs of the scales, which it is supposed to induce, are due to the hyperkeratosis which follows on the areated acanthosis.

More important for the pathogenesis of the affection than the primary epithelial changes, are the changes around the vessels of the cutis, although they do not so affect the external appearance. As in the papular syphilide, it is an infiltration of true plasma cells, surrounding the dilated vessels like a mantle. In order to see this, it is necessary to examine quite fresh spots, not larger than two millimetres in diameter. If they have lasted some weeks, the plasmatic character

of the new formation is only evident at the periphery, and not always even there, for it is a peculiarity of this process that the plasma cells very soon undergo a specific atrophy, so that their origin is indistinct. Therefore we must, in describing them, distinguish the fresh papules from those at the height of development.

In the former, the plasmomatic mantle on the dilated vessels, especially at the bifurcations, frequently shows thickenings, which are evident on sections as rounded areas. These areas may, in places, run together, but this does not affect the general areated and cord-like character of the new growth. As in the syphilides, the individual plasma cells of an area are alike in size and staining power of the protoplasm, only, this is here rather less; and in Ulerythema centrifugum there are none of the multi-nuclear cells and giant cells which distinguish the syphilitic plasmoma. Very rarely we find one plasma cell larger than the others; but it usually contains only one vesicular nucleus. It is also clearly distinguished from Lupus, for there are no pale multi-nuclear or giant cells. Consequently, even in this early stage, any confusion of these affections is unlikely.

At the acme stage, there can, with a good protoplasm stain, be no confusion, for here, at least in the centre of the affection, there are *no unaltered plasma cells.* Only the *regular* cubical or rounded form of the cells, and their oval, deeply-stained nuclei suggest their origin from plasma cells. There are, in particular, three points which indicate the proper character of the cells of this new growth, if it be impossible to examine younger spots. First, we find almost invariably at the periphery, a few intact areas of plasmoma; then all the lymph spaces of the central cellular areas are closely packed with protoplasmic fragments, staining like plasma cells, which always indicates their previous existence; and finally, the complete analogy of the clinical and histological appearance of this ulerythema with those later described, in which the plasmoma areas are always distinct, aids in decision.

Thus the cellular areas at the height of development are composed of cells, which at the periphery are almost cubical, in the centre, rounded; and all possess a large spherical, or ovoid, deeply-stained nucleus, inside the faintly-stained, pretty homogeneous protoplasm. The protoplasm surrounds the nucleus as a fine, regular shell; the contours of the cells are sharp at the periphery of the individual areas, in the centre often blurred, and sometimes nibbled and perforated.

A further main difference by which these cellular areas are distinguished from other plasmomatic areas, and brought nearer to the other ulerythemata, is the *central canalisation*, which commences in

the smallest areas, and enlarges with them, and always affects only their central parts. The enormous dilatation of the lymph spaces inside the areas, by which the canalisation is brought about, is most evident when every cell is fixed in its place by very careful embedding in celloidin. Then we see a winding system of tubes, which makes the area, in the centre, resemble a brushed-out lymph gland. These tubes are neither regularly cylindrical, nor clothed by a continuous endothelium. They pass, now into fluid spaces, now into spherical dilatations; sometimes they show a regular, flat endothelium, sometimes cubical cells of the area are arranged on them, or there are no cells at all.

FIG. 36.—Ulerythema Centifrugum.

H. Thickened horny layer.

H′. Horny taps corresponding to atrophic follicles, from which the sebaceous glands have disappeared.

P. Atrophic prickle layer. *C.* Canalised areas of infiltration.

O. Very œdematous papillary body, permeated at certain places by a fine net of fibres.

L. Cavities; pools of lymph.

This irregularity is evidently due to the fact, that certain cells, and collections of cells, constantly become free by the melting of the intercellular substance, and get inside the enlarging lymph spaces. If we carefully observe the canals, we see everywhere at their sides communicating spaces, which combine with other spaces inside the cell areas, and indicate how the lymphatic system increases at the expense of the breaking-up cellular area. The latter gains outside and around the blood capillaries, what solid cell substance it has lost in the centre and in the neighbourhood of the lymph capillaries.

It is clear, that these appearances very often look like endothelial proliferation in pre-existent large lymph spaces. I will certainly not deny a limited growth of the endothelia of the lymph and blood vessels, because I believe I have now and again seen it. But most of these appearances are due to *insulated liquefaction of cellular territories.* Very instructive are those appearances in which these islands of

tissue contain mast cells inside them, and are thus distinguished at a glance from endothelial growth. Otherwise, the mast cells share the peculiarity of all the connective tissue cells here, by rounding off, becoming more faintly stained, and at the border, often quite homogeneous, as if washed out.

The blood capillaries run through or around the areas, closely surrounded by cubical cells, and show here and there projections of their endothelium into the lumen, and proliferation of the endothelia. The collagenous tissue in the areas is very much rarefied; this rarefaction increases from the blood vessels towards the lymphatics. The breaking-up cells are only feebly fixed on the fine fibres. The elastic tissue has completely disappeared. Except for the fragments in the lymph spaces of the area, above referred to, which stain with protoplasm stains and are therefore albuminoid, and which I attribute to the washing out and homogenisation of the cell protoplasm, I have not found any other degenerations of the cells. In particular, I have never observed the fatty and colloid metamorphosis of the cells which is noted by almost all authors (the former on osmium preparations).

Equally characteristic as the existence of this central canalisation of the areas, is the fact, that at the height of the disease it has already reached its full development. It is therefore in no way a symptom of retrograde metamorphosis, but is as much an attribute of this cellular infiltration as are the paled and enlarged homogenised cells and giant cells of tuberculosis. But while there, a central degeneration occurs, which provides dry, firm products, we have here, a continuous breaking up of pretty well preserved, at most somewhat dissolved cellular elements, which lead to a pathological formation of cavities, and an irregular dilatation of the system of lymph canals. So that the cells in this affection are not particularly fragile, as one might conclude from their loose connection, but rather the inter-cellular substance completely yields, and instead of the spaces of the melting collagenous tissue (as in gumma) being filled up by vigorous proliferation of plasma cells, a more deliberate formation of cells leads to lymphangiectatic spaces inside the areas. As the firm, dry plasmomatic areas characterise the true plasmomata, so do the moist excavated ones the ulerythemata.

The œdematous character is at first limited only to the areas, but as the disease goes on, the whole connective tissue of the papillary body becomes œdematous and brawny, and the lymph spaces are much dilated, as are the lymph and blood capillaries. The collagenous tissue swells up in some places to homogeneous, hyalin-looking trabeculæ; in others it gives way, and we have, in addition to the dilated lymph capillaries, limitless, freely communicating pools of lymph. Some of

these, of the size of a quarter or half a papilla, margin directly on the epithelium, and there ensues a canalisation of the prickle layer; not only are the pre-existing lymph canals doubled or quadrupled, but some epithelial cells are lost, evidently washed away. Other epithelia of the lower, more rarely of the higher layers, undergo, like many connective tissue trabeculæ, hyalin or colloid transformation; but I have not been able to recognise a fatty degeneration of the epithelium, to which most authors refer.

The behaviour of the elastic tissue deserves special note. In contrast to the total disappearance which it undergoes in syphilis and in lupus, inside the nodules, it here remains—corresponding to the areated character of the cell-formation—preserved in many places; indeed it forms, as before, a connected net, in which the cellular areas only appear as large or small spaces. Thus we have, in the skin of the face, with which we mostly work, the normal elastic nodules persisting at the apices of the papillæ, under the epithelium. If, after the affection has lasted for some time, the œdematous swelling of the papillæ, just described, commences with partial tearing and partial stiffening of the collagenous tissue, the remains of the elastic tissue are gradually melted, and the last traces of these elastic nodules are found under the sub-epithelial border, as a series of homogeneous, bent and perforated clumps, which, with a protoplasm stain, look very like hyalin remains of connective tissue bundles, but which, with acid orcein, are seen to be remnants of elastin. We then see that they are often connected by processes with the remains of the elastic tissue of the papillary body. The true hyalin collagenous rafters show on the contrary, in addition to the different stain, a greater stiffness, are less bent and clumpy, and are not reticular.

The ectasis of the lymph vessels and lymphatics in the cellular areas, and outwards as far as the epidermis, the elephantiasic œdema of the papillary body with its lymph pools, all these changes which are regularly found in long-standing Ulerythema centrifugum, stamp the cutaneous tissue, and that of the papillary body in particular, as abnormally rich in water, and it is hardly possible to conceive a greater contrast than between this tissue and the cornified and strikingly dry epithelium, lying immediately above. All this takes place inside the few layers of the reduced prickle layer, by narrowing of the lymph spaces between the epithelia, but it is itself noteworthy, for it shows us that the degree of cornification is by no means only and importantly dependent on the amount of moisture in the prickle layer.

Now we know, that certain cases of Ulerythema centrifugum are distinguished by the œdematous character of their papules, that an inflammatory œdema of the border usually precedes the extension

of the area at the periphery, and that, on the other hand, the artificial induction of the latter usually leads to new eruptions. Therefore, in spite of the dry surface, the first rule of treatment is: **dry.** There are cases enough, which show microscopically, an extension of the œdema to the upper layers of the epithelium, vesicular dilatation of the inter-epithelial lymph spaces, which are filled with leucocytes, disappearance of the kerato-hyalin, crusting and splitting of the horny layer by the entrance of white blood corpuscles, and more or less saturation of the papillary body with them. But I do not regard the leucocytosis, any more than the vesicle and crust formation, as a part of the disease proper. They are only transient increases of the chronic process, in which the action of foreign external irritants can never be excluded. *Characteristic of the disease, in all cases, is only the arcated formation of the inflammatory cellular new growth, the disappearance of the latter and of the collagenous tissue in favour of the dilating lymph system, and the primary hyperkeratosis, with or without epithelial growth and its results; the œdematous changes, with hyalin swelling in the papillary body and prickle layer, and the formation of peculiar, plug-carrying scales, with stoppage of the follicles and ultimate atrophy of the cutaneous structures.* I would still say a few words as to the latter.

The cellular areas are, as already noted, mainly found on the surface of the skin, and are most common where epithelial growth and hyperkeratosis are most marked, thus on parts of the skin with lanugo hairs, and marked epithelial growth—like this—in the centre, and on hairy skin without epithelial growth, especially around the plugged hair follicles. From this seat of predilection, they extend downwards along the vessels, and surround, in areas, mainly the hair follicles, the larger sebaceous glands, and, very regularly, the coil glands. These more scattered, deep areas are, like the superficial ones, canalised, but a rare-fying œdema very rarely extends from them into the surroundings. They often last long unchanged, even if, on the surface, the disease is arrested spontaneously or artificially; they are often, of course, the cause of recurrences.

Apart from these inconstant, deep, scattered areas, which evidently are only very slowly absorbed, the disappearing affection on the surface shows, according to the affected region, different appearances. In very hairy regions, the hair cysts exfoliate, the hair follicle necks are shortened and flattened out, and the hair growth, if the disease has not lasted too long, is restored; the surface epithelium is thinned to a minimum, the papillary body is sunken by absorption of the collagenous substance, and the new hairs grow from a pale, somewhat depressed skin. On lanugo skin, many small hair follicles disappear altogether, from acanthosis of the surface, with consequent exfoliation; this is

why the scars always appear abnormally smooth and hairless. In addition to sinking of the papillary body, the disappearance of the collagenous substance, especially on the reddened parts of the face, makes the whiteness of the scar very apparent. As a fact, preparations of the healed centres from this region show, in the flattened papillary body, in addition to very much distended lymph vessels and lymph spaces clothed with endothelium, only scanty, narrow blood vessels at the seat of the sub-papillary net, and over it only very few capillaries; as the œdema disappears, many capillaries in this region are evidently occluded.

Kaposi described intense regressive metamorphosis of the coil glands and ducts; in the latter, the cells and nuclei are indistinctly margined, and dotted with dark granules; in the lumen of the former, there are vesicular structures, along with fat granules and fragmented epidermic masses, which are recognisable as far as the pore. These cases indicate the malignant form of the disease, of which I have no preparations. In the ordinary form, all the coil glands which are surrounded by plasma cells simply show a marked dilatation of the lumen, and complete preservation of the epithelia. In the lumen, there are often epithelia, containing deeply-staining granules, which resemble those described by me in Leprosy and Lupus, but do not resist acids. Groups of such granules are found free in the lumen and between the epithelia of the walls. Suspicion of micro-organisms is thus awakened. The lumen of the duct and the pore is often dilated, if the latter is closed by a dense horny plug in the epithelial ridge. I have not found in the coil apparatus more marked regressive metamorphosis.

Hæmorrhages occasionally occur in the tissue (Kaposi, Leloir), as is not remarkable, considering the thinning of the vessel walls. I have not found Leloir's Endoangioitis obliterans, or any new formation of blood vessels, in my preparations.

Mast cells are not more frequent than normal; in the centre of the areas, as already noted, they are unusually small, rounded and less stained. But as healing proceeds, they increase, and show once more their normal form and stain.

From this description of Ulerythema centrifugum, a confusion with lupus of the skin is histologically so completely excluded, that it is unnecessary to make any differential diagnosis.

From these appearances of the ordinary eruptions of Ulerythema centrifugum, there is a slight and readily understood deviation in the *pernio-like papules* of the fingers (so-called Lupus pernio). I have twice had the opportunity of examining these, and have noted the following. The most marked appearance is the great hyperkeratosis, which has led, not to a fine scale with a few horny protuberances, but

to a regularly firm callosity, most dense in the centre. This is almost completely homogeneous, shows only few nuclei, and no areas of nuclear fragments or other products of inflammation. The granular layer under it is normal in breadth (on the finger pulp three rows), but often more feebly developed and finely granular, even to the disappearance of the granules in the centre of the papule. The supra-papillary prickle layer is thinned, and contains few wandering cells, although its inter-cellular spaces gape. The inter-papillary ridges are diminished, run at acute angles to the cutis, and are—which is very unusual here —very irregularly bent. Here, also, there are a few leucocytes in the gaping lymph spaces; but there are no mitoses in the whole prickle layer.

Corresponding to the thinning of the supra-papillary, and the bending of the inter-papillary prickle layer, the papillæ are considerably thickened by œdema and cellular growth, and their flattened, broad heads sometimes unite. There are found in them a few plasma cells, but otherwise, around the blood capillaries, only round, atrophic connective tissue cells, of the type characteristic of the disease. The lymph vessels are dilated and filled with plasmatic fragments, but in contrast to the ordinary appearance of Ulerythema centrifugum, the lymph spaces are not; and we do not find the pools of lymph at the margin of the epithelium, or any true canalisation of the connective tissue. The œdema leads as a rule only to a brawny loosening of the whole papillary body.

In the thinning and atrophy of the prickle layer, between the hypertrophic horny layer and the thickened papillary body, and in the nature and distribution of the cells, we find once more traces of the ordinary form. But the whole papule is dry, and is under increased pressure, so that many of the peculiarities of œdema are awanting.

The purest contrast to this variety is *Ulerythema centrifugum papulatum*. I had the opportunity of examining a typical case of this, from the cheek of a girl. There were found, to put it briefly, just the ordinary histological appearances. Even in the œdema of the cutis, there were none of the expected differences. I must therefore regard this variety simply as the combination of a *spastic œdema* with an otherwise unchanged Ulerythema centrifugum. It is easy to understand, that if an urticarial œdema, limited to the affected spots, appear, the skin with its dilated lymph spaces must very readily swell up into elevated white papules, without, as in ordinary urticaria, the new lymphatics, which have induced the spastic œdema, being evident in the excised piece. This variety illustrates very well, that a local infectious disease of the skin may produce, in addition to changes in texture, local, persistent angio-neurotic effects.

Ulerythema sycosiforme.

This affection begins in the beard or in the temporal region, with flat, elevated, sharply-margined erythematous spots, on which superficial vesicles, crusts and scales are formed. It extends serpiginously, with red, somewhat elevated borders, following the course of the beard, and it also attacks the region of the cilia and supercilia. It has a very chronic course, little influenced by treatment, and finally leads to the formation of completely hairless, smooth, white, somewhat depressed, scarred-looking, atrophic surfaces, covered with a finely folded horny layer. The addition of impetigo may make it appear like a coccogenic sycosis, but the atrophy of the cutis in this affection is never a result of suppuration, and the disappearance of the hair is only a manifestation of the atrophy of the whole epithelium. Therefore there are found, on the scarred surface, no depressions corresponding to the follicles. Clinically, we can distinguish an initial stage of simple erythema, an intermediate acme, and a final stage of definite atrophy.

Sack examined a typical case in my laboratory. In contrast to Ulerythema centrifugum, there existed here, at the height of the process, a widespread plasmoma, which was primarily and mainly distributed around the hair follicles, surrounding them in their upper parts with a smaller, in their middle and lower parts with a broader girdle, and deeper down, running together by numerous reticular processes, to a more diffuse cellular infiltration. Where the plasmoma is developed, the elastic tissue completely disappears, while the collagenous is much rarefied. In preparations stained for elastin, the disappearance of this substance is very remarkable, if one compares it with normal preparations of the skin of the cheek, for these are very rich in elastin, and on the surface at this region, we have the very characteristic elastic nodules. On account of the disappearance of collagen in the neighbourhood of the plasmoma areas, Sack is inclined to consider that the fibrillary substance is used up by the plasmoma cells, and names them : fibro-clasts. I regard disappearance of collagen and plasmoma as the effects of one and the same cause, and do not believe that the former is the result of the latter ; for there is a number of plasmomata, which are accompanied by the hypertrophy of the collagenous tissue instead of the disappearance.

To the cellular hyperplasia of the cutis there is early added an atrophy of the epithelial structures, which in this region are mainly represented by hairs and sebaceous glands. The sebaceous glands disappear in the ordinary way, by the simple arrest of the sebaceous metamorphosis of the cells, the hairs pass into the bed hair stage, and the lower parts of the follicle are not filled up by young epithelial processes, but they atrophy. We find transitions of hair follicles with fine remnants of hairs, to thick, and finally to fine epithelial processes,

without a trace of hair. At the same time, as the follicular epithelium more and more disappears, there is found, in the surface epithelium, an attempt at a new production of hair, in the form of young mitotic epithelial depressions, unconnected with the remains of follicles. But this does not go on to the formation of hairs, and the acanthosis of the surface only leads to the formation of a more abruptly wavy ridge net and papillary body, than is usual in this region. In some places the attempt at formation of new areas is indicated by fine, long epithelial processes, whose ends are indented by very small papillæ. When the affection concludes with a scarred, atrophic, hairless surface, the surface epithelium is always much more developed than normal, and retains the ridge formation, as the surface of the cutis does a feebly developed papillary body, while the luxuriantly developed elastic net of the latter is not again formed. The coil glands and muscles of the skin also undergo atrophy. In addition to the typical plasma cells, of which we can distinguish very large, medium and small ones (plasma daughter cells), there are found, in the papillary body, pretty large quadruple and quintuple nucleated chorio-plaques, pretty numerous mast cells and simply enlarged spindle cells.

In addition to these progressive and dry regressive changes, which would explain the initial swelling of the skin, the atrophy of the hair, the rarefaction of the cutis, and the later scarred depression, we find important circulatory changes, which lead to the clinical symptoms of erythema, scaling, and vesicular formation, and aid in the ultimate resorption of the cellular infiltration. Even at the commencement, we meet a marked dilatation, partly of the papillary circulation, partly of the peri-follicular vessels. The plasma cells are chiefly formed along these vessels. As in Ulerythema centrifugum, there soon takes place a gaping of the lymph spaces inside the cellular infiltration, due to the absorption of portions of, or of entire plasma cells, near the lymph spaces. The latter lose, as in that affection, their granular protoplasm, which we find again in the form of granular material of the same staining power, in the lymph spaces; or the protoplasmic body is converted into a small ring of protoplasm, the whole cell into a small plasma cell, which, however, is always easily distinguished from a white blood corpuscle. The cellular areas, permeated by wide lymph spaces and lymph vessels, are always characterised by the varying size of the cells, and are distinguished, both by this and by the permanence of the plasma cells during the continuance of the process, from the similar cellular areas of Ulerythema centrifugum.

Around the hair follicles in particular, the dilatation of the lymphatics leads to a very loose arrangement of the tissue; the follicular epithelium in the still preserved papillary hairs is often

directly surrounded by lymph pools in the cellularly infiltrated follicle wall, and here only does a marked emigration of leucocytes occur into the prickle layer of the hair follicle and the hair fissure. Consequently, the epidermis is permeated, in the immediate neighbourhood of the follicle, by a moderate number of leucocytes, but more by a sero-fibrinous exudation; the epidermis is parakeratotically altered, and the horny layer replaced by a fibrinous scale. There is no doubt that these acute, exudative, inflammatory changes, limited to the neighbourhood of the follicle, correspond to the periodic scaling, vesicle and crust formation of this affection. There does not appear to be any special significance in their course. But there is in the persistent œdema of the skin.

This gradually attacks all the cellular infiltrations, the individual cells are washed out, and finally washed away; a wide lymphatic system appears, instead of the firm fibrillary and elastic tissue, and this introduces the diffuse disappearance of tissue, which goes on to complete atrophy. It is evidently these regressive changes also which induce the general conversion of the papillary hairs into bed hairs, and the transformation of these into unproductive epithelial processes.

This œdema, which removes the cellular infiltration, and is caused by the breaking down of the cells and disappearance of the collagenous and elastic tissue, stamps Ulerythema sycosiforme as a true Ulerythema. It characterises, along with the plasmoma and the hyperæmia, which alone are present at the commencement, the acme of the disease.

Ulerythema acneiforme.

I have investigated the only case of this rare affection. On both cheeks of a young girl, there appeared red, flat, somewhat elevated papules, inside which comedones developed; the redness again disappeared, and the skin became white and scar-like. The process affected both lobes of the ears, and it healed with an irregular epidermis, and a branched, grooved scar on the border of the ear, leaving behind large comedones in the lobules. At the border of the antitragi and the cheeks, there was found a peculiar superficial scarring, without comedones, which gave the skin a worm-eaten appearance. A number of peculiar large comedones, without any scarring, crossed the scalp from one ear to the other.

The excised pieces show three stages of the affection. The commencement corresponds clinically to the erythematous papules, with universal hyperkeratosis and comedo formation, found on some parts of the border. Here there is general hypertrophy of the prickle layer, but especially of the mouths of the follicles and sweat pores, with the formation of irregular ridges and taps. The coil glands remain normal, only their lumina are dilated. The blood vessels are also dilated.

The cutis is permeated by circumscribed cellular areas, having no relation to the vessels, and in which the collagenous substance is reduced to a net of fine fibrils. These areas consist of round, large nucleated cells, which contain only little granular protoplasm, and show a few rounded mast cells, and no plasma cells. They are penetrated by a quantity of large, communicating lymph spaces.

The height of the affection, corresponding clinically to the pale, depressed, comedo-covered spots, is characterised by the fact, that the acanthosis extends, but is exceeded by an abnormally severe hyperkeratosis, so that, after the disappearance of the lanugo hairs in the sebaceous glands, the widened hair follicles contain little but concentrically arranged horny pearls. By this almost completely cornified, broad and deep epithelial depression, the cutaneous tissue is very much reduced; the otherwise normal coil glands thus appear to lie unusually superficially in the cutis. This is, in almost its whole extent, occupied by a cellular infiltration, of the character described, permeated by numerous gaping lymph spaces; the collagenous substance, breaking up and dissolving, consists partly of fine fibrils, partly of coarse, weather-beaten rafters, and finally of short, thick, irregularly distributed remains of normal thick trabeculæ, which stand out clearly with an orcein stain. The elastic tissue is, at the seat of greatest cellular infiltration, atrophic, but in other places, and especially at certain parts of the surface, it is normally developed, and here forms the striking, thick elastic nodules, which distinguish the normal skin of the face, especially of the cheeks.

The regression, clinically corresponding to the circumscribed cutaneous atrophies, with shallow furrows and deep grooves, is indicated by the falling out of the comedo-like horny pearls and horny plugs, from the thickened and almost completely cornified epithelial taps, epithelial ridges and horny degenerated follicles. There thus develope those rills and grooves which are separated by persistent cutaneous ridges. The cellular infiltration is mostly absorbed, only remaining around the dilated lymph spaces. Thus the greater part of the previously atrophic collagenous tissue has disappeared; the whole cutis has lost in volume, and is depressed and scar-like. The elastic tissue has also for the most part disappeared, the cutaneous muscles, which are present in abundance in the skin of the face, persist, as do the coil glands.

We have therefore in this affection to do with a cellular infiltration of the cutis, which, even at the commencement, and still more at the height of development, shows the same character as the other Ulerythemata; that is, it is distinguished by the simultaneous disappearance of the collagen, and the striking dilatation of the lymph spaces inside

the cellular infiltrations; atrophic changes, which, after the disappearance of the cellular part, are manifest in the form of scar-like atrophy. At the same time there is distinct hyperplasia of the prickle layer of the surface and the follicles, with consecutive, marked hyperkeratosis, so that the affection, externally, somewhat resembles Acne vulgaris. From that it is distinguished—apart from the different localisation, which is more that of Ulerythema centrifugum—by the primary inflammatory erythema, the complete absence of suppuration, and the scarring atrophy, due not to suppuration and breaking-down, but simply to interstitial absorption, by the atrophy of the sebaceous glands, and the consequent purely horny character of the horny plugs, by the œdematous cellular infiltration, and the absence of plasma cells and giant cells, as well as by the absence of the characteristic organisms.

From Ulerythema centrifugum this affection is mainly distinguished by the more marked acanthosis and hyperkeratosis, and the marked affection of the follicles; from Ulerythema sycosiforme also by the marked acanthosis and hyperkeratosis, and by the absence of true plasma cells.

Ulerythema ophryogenes.

This affection, which was first described by Taenzer in my clinic, occurs mainly in blonde individuals. It affects always and preferentially the eyebrows, extends over the adjacent parts of the forehead and cheeks, to the neck, and often appears again on the extensor sides of the upper arms. In certain very severe cases, it extends from the forehead to the hairy scalp. In the milder degrees it is merely a persistent erythema, with the elevation of very small horny globules at the mouths of the hair follicles. The affected hairs are broken off close above the surface, and are abnormally fine, or invisible. On the outer parts of the eyebrows, and on the upper arms, the changes in the follicles predominate; on the forehead, cheeks and neck, the inter-follicular erythema. After years of persistence, the affection leads to follicular and inter-follicular atrophy, in the form of small, scar-like depressions, which stand out clearly from the hyperæmic surroundings. The outer part of the eyebrows completely disappears. In the most marked cases there are also found atrophic areas on the cheek, the forehead, and the upper lip, which are completely hairless, while the atrophy of the scalp may also lead to the loss of a great part of the hair. The individual hair circlets are enclosed by a scar-like, hairless, smooth zone, while the centres of the hair circlets still contain a few abnormally dry hairs, on a hyperæmic base. Many cases remain throughout life at the stage of erythema and horny globules. Except for the atrophy, the affection resembles Keratosis suprafollicularis.

I have three pieces of skin from a typical case in a young man, whose eyebrows with their outer parts were already scarred; one a pale papule with a horny plug from the arm, a piece from the erythema of the forehead above the eyebrows, and an atrophic

piece of the eyebrow itself. The two former represent the slighter initial form, the latter the ultimate form, of moderate degree; I have not been able to procure a specimen of the complete atrophy of the skin, such as occurs in the scalp.

(a). *Erythema.*

The blood vessels of the central cutis and of the papillary body are all much dilated; their walls are hyper-nourished and cellular. The dilatation is most marked around the follicles. The collagenous tissue, like the elastic, is, in general, normal; only the tissue immediately around the follicle is altered. The collagenous substance here is somewhat rarefied, and the lymph spaces correspondingly dilated. There is no marked cellular infiltration. The perifollicular collagenous tissue is less wavy, the bundles less rounded, and sharper; the whole looking like the commencement of a sclerosis. The connective tissue of the hair follicles takes a diffuse bluish colour, with the usual hæmatoxylin stain; it is therefore altered in texture. The mast cells are increased in number.

The ridge system of the epidermis is somewhat wider than normal, but mitosis is rare. The granular layer is well developed, the horny layer, as a whole, normal, but in places somewhat widened, usually so at the mouths of the follicles. From here, slight hyperkeratosis extends through the two upper thirds of the hair follicles. The mouths of the follicles are usually narrowed, and closed by a small horny plug, as in the flatter form of Keratosis suprafollicularis (so-called Lichen pilaris), and just as there, though not so regularly, there may be formed horny cysts in the upper third, and irregular spiral windings of the middle third, with retention of the spirally twisted hair in the peripheral segments of the prickle layer of the hair follicle. But there are certain differences in these phenomena of retention; the horny cysts here are rare, usually small, and seated not directly underneath the horny plug, but deeper. The spiral twisting of the hair and hair follicle is usually less, the hair is of finer calibre, and rarely observable in the upper part of the follicle; this is no doubt due to the abnormal collection of horny layer over the whole prickle layer of the hair follicle, down to the under third. We meet now and again with hair follicles, which, instead of hairs, contain a regularly thick horny cylinder, in which the hair is absent or difficult to recognise. In some more resistant hair follicles, there are coarse, mechanical changes; I found a hair follicle, in which the hair, after making a spiral twist in the middle segment, described a curve in the under part, and, loosened from the papilla, was evident much further above, with its root placed

laterally. Certainly, the erythematous initial stage of Ulerythema ophryogenes is by no means easy to distinguish, microscopically, from the erythematous form of Keratosis suprafollicularis. Most weight must be laid on the peri-follicular rarefaction of the connective tissue with sclerosis, and the absence of peri-follicular cellular growth.

(b). *Horny papule.*

The blood vessels in this form are not dilated, but are somewhat more cellular than normal. But the rest of the cutis is not. The connective tissue around the hair follicles, and these themselves, show the same changes as in the erythema : slight sclerosis, and abnormally wide lymph spaces. The epithelium is also somewhat thicker than normal, but the hyperkeratosis above the follicle mouths is much more marked than in erythema. From here, a widened horny layer extends into the follicles. The centre of the papule is formed by such a follicle, distended by the horny layer, in which we can distinguish an upper swelling, corresponding to the infundibulum, and an under one, corresponding to the middle part of the follicle, so that the whole horny cyst has a barrel shape. In the centre, a fine hair is visible.

To this corresponds, in Keratosis suprafollicularis, the anæmic form with the horny cones, and there also this analogous form tends less to spiral twisting of the follicle, and to the formation of hair spirals. From the corresponding papules of Keratosis follicularis, those of Ulerythema ophryogenes differ—apart from the regressive changes of the connective tissue—in the deeper penetration of the hyperkeratosis to the under third of the follicle, and the cylindrical or barrel shape of the two upper thirds. The under third now and again sends off irregular, small, lateral buds, but only rarely do we find along with a bed hair, a productive epithelial process.

(c). *Atrophy.*

In the atrophic piece of skin, the hyperæmia has completely disappeared ; the vessels are not only narrow, but are scanty and poor in cells. The superficial layers of the cutis also contain few spindle cells ; mast cells are not found at all. The connective tissue around those follicles which contain horny cysts, as well as around the numerous sebaceous and coil glands, is sclerotic, penetrated by wide lymph spaces, and relatively poor in cells. The surface epithelium is normal, but that of the follicles is markedly atrophic. Those follicles which are not changed in the hyperkeratosis, are distinctly diminished ; their lanugo hairs have mostly fallen out. In their place, we find simple epithelial processes with small papillæ, or—and this is very frequent

—large sebaceous glands. The sebaceous glands occupy much more space in the cutis of the eyebrows than usual, and the skin resembles rather that of the nose, or that in seborrhœic baldness. The coil glands also are altered in form, the loops are enlarged, bent and distorted. Close together in the under part of the skin, these glands lie embedded in rarefied, sclerotic connective tissue.

These observations give us an idea of the pathological process, which attacks the skin through the hair follicles. The follicles are closed, and deep hyperkeratosis of the follicular epithelium takes place. In some regions, the horny production of the follicles predominates, in others, the accompanying diffuse erythema; and in these cases are mainly formed the secondary spiral deformities of the hair and follicle. With these changes, which closely resemble the analogous but not identical ones of Keratosis supra-follicularis, is combined, in the slighter degrees, a sclerotic change of the peri-follicular connective tissue, accompanied by dilatation of the lymph spaces. This latter is shown later, in the inter-follicular parts of the cutis, by the regression of the vessels, and the originally moderate cellularity; and in cases of great atrophy of the scalp, it probably goes on to atrophy and sclerosis of the whole cutis.

Ulerythema ophryogenes differs very importantly from Ulerythema centrifugum and sycosiforme. For here, in the stage of erythema, no cellular areas are formed, to say nothing of diffuse plasmoma. The atrophy of the collagenous tissue, which, together with the atrophy of the vessels, causes the scarred appearance, occurs without any previous new formation of cells, and the single connecting link between this Ulerythema and others histologically related, is the rarefaction of the collagen, and the dilatation of the lymph spaces.

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Alopecia areata (Area Celsi).

An affection of the hairy skin, commencing on the head, usually limited to it, and rarely becoming universal, in which round, sharply-margined, concentrically enlarging, non-erythematous bald spots appear. The spots show first a loosening of the hair, then, somewhat suddenly, a breaking off, 3-6 millimetres above the surface, and the loose remainder has a thicker, darker, upper end, which gives to the area stumps the characteristic form of a point of exclamation. Very soon after this, we find the spot itself quite free from hairs, but at the border we find the typical stumps, which alone justify the diagnosis. After the falling out of the hair, there is always a slight, perceptible depression of the skin, but only after years is there a scar-like persistent depression. The course is chronic, with long remissions and relatively rapid relapses and improvements. But, even after years, the normal hair growth is almost always restored. The sensibility of these places is normal, the irritability and power of inflammation diminished. Characteristic of this distinctly contagious, often distinctly epidemic disease, is the absence of the familiar, easily recognisable fungi of the scalp (Tricophyton, bottle bacillus), and of inflammatory epidermic changes (vesicles, scales and crusts), at least in the ordinary, pure cases of Area.

The micro-organism of this disease is still unknown, although the disease is certainly contagious, and a whole series of different fungi have been discovered since 1843 (Gruby). I run over them shortly, though in years of investigation, even with the application of the best methods of staining, I have not been able to confirm their existence. Gruby describes fungi with numerous branches and spores on the surface of the hair; that cannot have been Area. Stein (1860) found the fungus, which Gruby described as microsporon, in a cat, but not in man. Malassez and Courrèges (1874) described different spores without hyphæ, which occurred, not on the hair, but in the epidermic cells in the neighbourhood of the spot; their two first varieties are vegetation forms of the bottle bacillus; they also cannot have investigated pure cases of Area, for it is characteristic of that, that with few exceptions, the ordinary epidermic flora of the head are absent.

Buchner (1878) found, by repeated cultivation from one case, a fission fungus, a granule 1μ in size, with two very short, thread-like processes.

Eichhorst (1879) found—though only in nine cases—spores, on the surface of the hair, and between the hair and root sheath, which were 3·5 to 4·0μ, rarely 1·3μ, in size, and arranged in groups, sharply margined; here also I think we must assume a complication of Area with Pityriasis capitis (bottle bacillus).

The only positive results connected with the new staining methods are those of v. Sehlen (1881). He found in the follicle neck, more rarely deeper in the follicle, collections of very small cocci (0·3-0·5μ)

between the hair and the root sheath; in agar cultures they were somewhat larger (1·5μ). Thin, who found simultaneously an organism between the hair and the root sheath, later identified this "bacterium decalvans" (1885) with v. Sehlen's cocci.

The cocci, and the cultivation results of v. Sehlen, are, in view of his preparations and cultures, not to be denied, but it is still questionable whether he was dealing with pure cases of Area.

I have investigated a great number of cases, partly in stumps, partly in sections, and have determined, in the majority of them, the complete absence of any fungi recognisable with our present methods, in the regions to which v. Sehlen refers. In some cases, and always where there was a complication with seborrhœic catarrh, I found, like v. Sehlen, at the level of the infundibulum, bacilli on the surface of the hair, and now and again, also morococci; but they were present only in some hairs, and there were no cocci which I could identify with v. Sehlen's.

More value is to be laid on the discovery of fungi in the lower parts of the follicle, and I have recently determined, in all cases of Alopecia areata, the existence of very small, plump bacilli ($\frac{3}{4}\mu$ broad, $1\frac{1}{4}\mu$ long), which also occur on healthy hairs. They are seated in masses on the hairs of the first stage (which are indicated by a gradually pointed, atrophic, hollow root), and cover a great part of the intrafollicular end of the hair, close down to the point of the hair root; they penetrate also under the cuticula and into the remains of the root sheath, but not into the hair substance. They are also found in the bed hair roots of the after growth. But I cannot lay any etiological value on these bacilli, for they also occur in the healthy.

Compared to the considerable literature which has developed on the etiological question, now bacteria, now nervous disturbances, and of which we can only consider the bacterial observations, which at least are positive, the histology of Area has been somewhat cavalierly treated. The older authors contented themselves with the investigation of extracted hairs, and their observations are by no means without interest. But one can only make things clear, by separating the hair roots, according as they represent original papillary hairs altered by the process, or the after growing bed hairs. Then only do we understand the contradictions which occur among authors (see, for example, the complete summary in Plattner, pp. 37-48). Both forms of the hair are more easily extracted than is usual, but the first variety is very much more easily extracted than the papillary hairs generally.

This first form is found only immediately around the area; only when the hair is little disturbed (Dispensary patients), is it also found at the margin, and scattered over the surface. These hairs are normally

shiny, do not break off and split up, but they are easily extracted, and show a gradually diminishing, pointed root, exhibiting no distensions, and neither excavations nor a conical, solid bulb.

The hollow root is atrophied to a fine point, on which one only exceptionally sees the slight impression of a diminished papilla. In better class patients, who attend more to the hair, these hairs are mostly removed.

The second form of Area hair roots is got only on the Area itself, usually at the margin towards the healthy growth, and varying in number, according to the amount of brushing. They are usually broken off 5-10 millimetres above the surface, and look exactly like points of exclamation, since, towards the follicle, they not only get smaller, but also distinctly paler. The broken part is very often abnormally dark, sometimes as black as coal. Usually this blackness gradually disappears downwards, sometimes it is suddenly arrested. This diminishing shaft passes into a normal, but very small, solid root, but in many cases it shows one or more swellings, both in the extra- and in the intra-follicular segments. Both at the thick end and in the intercalary swellings, the medullary canal is distended by a central collection of air (Spiess, Behrend). Evidently the breaking of the hair, the stump formation, is due to this. The stumps resemble, macroscopically less than microscopically, those of Trichorrhexis nodosa. But the brush-like end is usually much shorter and more irregular than in that affection, and the hair substance is darker. The brush-like appearance is often completely absent, and instead of this, the hair is split up for some distance, or still more often, broken off square. On the distended parts, underneath the rupture, the commencement of the splitting is sometimes noticed in a lateral defect. Both at such places, and at the broken end, there are found, in addition to black granules of pigment, the most varied saprophytic fungi. In these solid roots, which correspond to bed hairs, I have often found the bacilli above referred to, closely over the root. It is these hairs to which the often-used epithet, "opaque," applies, and when they show distensions they are "brittle"; only, these ones, though neither more nor less than all bed hairs, often have with them part of the prickle layer of the hair follicle, while all these peculiarities are not found in the atrophying ends of the first stage.

From the histological investigation of these hair roots in Area Celsi, it is clear that, while we are dealing only with atrophic changes of the hair, we must distinguish two distinct forms of regressive metamorphosis: an acute, affecting only the root of the previously normal papillary hair, and which represents the commencement of the whole process; and a chronic, which affects the hairs which persist for

a long time as bed hairs, not only on the affected solid roots but on the hair shaft above, and which may last an indefinite time. Only the latter changes resemble those of Trichorrhexis nodosa ; the former are more comparable to the atrophy of the root of the papillary hairs in other acute Alopeciæ (Alopecia syphilitica, Alopecia postfebrilis, etc.).

The investigation of sections is comparatively recent, and the most valuable works are those of Harris, Robinson, and Giovannini.

Harris, in a specimen from the corpse, found the hair follicles and sebaceous glands atrophic, but the coil glands normal. An infiltration with new formed cells reached from the centre of the cutis to the papillary body, and surrounded the hair follicles, blood vessels, and the capillaries of the papillary body. The atrophic hair follicles showed more epithelial buds than usual, and the transverse muscle also was much thickened. Immediately around the atrophic hair follicles, there was hypertrophy of the connective tissue.

Robinson investigated seven cases during life, and always found appearances of inflammation, as well as a perivascular, but not very widespread, and *not specially peri-follicular* infiltration with round cells. In recent cases, the lymph had coagulated in the dilated lymphatics, and some of the larger and smaller arteries contained thrombi. In older cases, the blood vessel walls were always thickened. In all the lymph spaces of the cutis, Robinson found cocci, numerous in recent cases, and these he regarded as the cause of the affection. The cocci were about the size of the staphylococcus aureus ($0{\cdot}8\mu$). (In the original this is misprinted 8μ.)

The epidermis in all cases is normal, as are the coil glands. The changes of the hairs themselves are, according to Robinson, not very different from those which occur in the normal casting of the hair. In recent cases, they only of the appendages of the skin are affected ; later, the sebaceous glands also atrophy, and very late, the fatty tissue. Robinson thus does not attribute the depression in Area—like Michelson—to the disappearance of fat, but rightly—like Hutchinson —to the absence of hair. Robinson recognises primary changes in the blood and lymph vessels, and regards the later glandular atrophy as the result of a chronic obliterative disease of the vessels, and the casting of the hair at the commencement, as the result of an acute thrombotic closure of the arteries.

Giovannini's works on the histology of Area Celsi are very valuable. In his principal work, he describes the results of the examination of twenty living cases, using a staining method (gentian violet, decolourisation with chromic acid) which permits of the study of the finer changes of the horny substance of the hair shaft. In spite of the value of this careful work, in which the ideal appearances of the hair

follicle were reconstructed from a series of cross sections, and in spite of the conclusions in regard to the occurrence of mitosis and cornification in the individual segments of the hair, I regard his conclusions as to the inflammatory changes, as open to dispute, as I do those of every investigator who only uses material fixed in Flemming's solution.

Giovannini lays most value on what he thinks the definite proof that an infiltration of white blood corpuscles around the deep part of the hair follicle, not only accompanies the affection, but precedes the other phenomena. In contrast to his predecessors, he regards Alopecia areata as, in the main, a deep-lying folliculitis. To this local leucocytosis, he ascribes the degeneration of the hair substance, by the connecting link of a peri-follicular disturbance of circulation, which first influences the nutrition of the hair, and then leads to the death of the matrix of the hair. I must note here at once, that, even if the constancy of a primary leucocytosis in and around the under segment of the follicle were clear, which to my mind it is not, the conclusion that such a leucocytosis suffices to explain a degeneration of the hair bulb, by no means follows. For there is a whole series of inflammations of the skin, with marked leucocytic immigration into the hair follicle (certain cases of coccogenic sycosis, trichophytosis, and many accidental discoveries in inflammatory dermatoses), which never lead to loss of hair, to say nothing of a necrosis of the bulb. Giovannini too readily ascribes all the nuclei in Flemming preparations to leucocytes. Usually this "leucocytic" infiltration accompanies the degeneration of the end of the hair; exceptionally, there is found a marked degeneration, with slighter infiltration. Were Giovannini's assumption, that the leucocytic infiltration causes the degeneration, correct, at most the opposite, slight degeneration with severe infiltration, might occur. I have, like Harris and Robinson, found numerous markedly atrophic follicles, with almost no cellular infiltration around the deep part of the follicle.

After these critical notes, I will state those results of Giovannini which appear to me of permanent value. He very correctly distinguishes two stages of the affection; in the former, the hairs are loose and partly broken, in the latter, they fall out and are replaced by an insufficient after-growth. At the commencement, we find a cellular infiltration around the vessels of the under part of the follicle, most marked above the bulb, often only unilaterally seated on the follicle, like a node. The hair papillæ often show the same. On the upper part of the follicle, only in two places is there found a cellular infiltration, viz., underneath the sebaceous gland, and underneath the infundibulum; in a word, where the vascular loops come nearest to the hair. The vessels of the superficial circulation are in general

surrounded by a cellular infiltration, the lower ones only in patches in the neighbourhood of the follicles. The intermediate skin is only moderately infiltrated, more in the upper part than in the under. The coils are always free from infiltration, while that is present around the upper parts of the duct. At the same time, the mitoses which are normally found in the hair matrix disappear, and the pigment increases.

All this I can confirm, with the proviso that the cellular infiltration is not of leucocytes. More of this anon. The first sign of disappearance of the hair inside the follicle is, according to Giovannini, the numerical diminution of mitoses in the matrix; these do not disappear, but are rapidly reduced to about a fourth of their number. Then the cells of the matrix of the hair and the root sheath degenerate, the nuclei are less granular and stain less, and finally the cells are converted into formless fragments, while the pigment in and between the cells disappears. The solution of the matrix cells leads to destruction of the bulb. But further, the supra-bulbar part, the "neck" of the hair, also degenerates, sometimes becoming thinned, sometimes showing discrete areas of degeneration. Ultimately, it also disappears, atrophying from beneath. Then only does the root sheath of the bulbar and supra-bulbar part disappear, having previously broken down into its individual cells. Thus the connection between hair and follicle is broken, and the hair falls out.

Since in this description Giovannini always speaks of degeneration, destruction and solution, I suppose I interpret him rightly if I assume that he regards the diminution of the Area hairs as a *necrosis* and *absorption* of the *deepest epithelia, in situ.* My preparations have rather led me to agree with Harris and Robinson.

The diminution of the deepest parts of the hair before its casting, is only a simple atrophy and displacement, such as occurs normally, and the peculiarities, the irregularities, of the end of the hair are explained by the greater intensity and rapidity of the process in Area Celsi. My investigations have been made, in addition to numerous hairs, on three pieces of skin, two from the living, one from the dead, the latter of which I owe to the kindness of Dr. E. Fraenkel. I, like Giovannini, examined some horizontal sections, but mostly the ordinary vertical ones. To sum up the results of the three cases—the first sign is disappearance of the bulb; with the disappearance of the epithelial new formation, the epithelial cap surrounding the papilla becomes less, both in height and breadth. At the same time, the papilla diminishes and acquires the form of a spherical button, and the homogeneous membrane becomes thicker. While those changes only occur slowly in the ordinary casting of the hair, and lead to the fact

that the papillary hair leaves the papilla just as it has come on to it, in Alopecia areata the leaving occurs later, and then suddenly, with a jerk. Even before the casting of the hair, the under end thins, especially in the rind substance, while the medulla is now and again (Giovannini) dilated, and cavities are formed by the taking up of air. If the epithelial after-growth is completely arrested, and thus there is no force pushing it outwards, the under end cornifies much more than usual. Thus we have an abnormally thin piece of root, which at its under end is less pointed, but as a whole, is firmer than usual. This is of course seated more loosely than usual in the relatively too wide follicle, and is therefore readily removed; thus it is that we find these hairs cast off in abundance, but rarely in sections. The abnormally deep cornification is not always regular. There are spaces in the cornification of the root sheath, into which, as a place of less resistance, the softer cells of the resisting matrix of the rind and the medulla are pressed; or the cornified root sheath cells sometimes completely yield, and are scattered among the less cornified central epithelia of the hair ends.

Thus I find histological differences between the cast hairs of normal skin and of Area, mainly in two points; the Area hairs are more deeply cornified, are thus thinned, and they form no regular, fibrillated, brush-like roots, for the root sheath does not normally arise before the hair, but with it. The irregularities of cornification of the end are too rare to be regarded as typical. Whether they have any relation to the areas of degeneration described by Giovannini, I do not decide. I found in the foci no special degeneration distinct from the normal epithelial atrophy in the casting of the hair, and in cornification.

Further, I must note that, in addition to this abnormal method of casting of the hair, the normal casting occurs in many hairs, with slower advance of a brush-shaped end as far as the middle follicle region, and with subsequent bed hair period. These hairs are oftener found in sections than falling out, for they are not so loose. It is in them too that the secondary regressive metamorphoses, which have some resemblance to Trichorrhexis nodosa, appear. They further supply one of the proofs of the possibility of the growth of the hair from the hair bed, for we here frequently find point-of-exclamation-like, longer hairs, which at their outer end are medullated, and therefore are old papillary hairs, but which have a long, homogeneous, light, thin, non-medullated root portion, which can only be supplied by the brush-like solid root, for the thin hair ends of the acute period directly lead to casting. Above this they are dark, and show distinct cuticles.

From the relatively sudden casting of the papillary hair, after it has,

being seated in the whole length of the follicle, undergone a thinning of the root end, it is explicable why the follicle, which collapses after it drops out, is distinguished from that in the normal casting of the hair, by its greater length. It has not, as usual, become shortened during the ascent of the papillary hair, nor has it given the opportunity of forming a more or less narrow connective tissue process (Haarstengel). Thus it is, when, in the casting of the hair, remains of the matrix are left and produce a young hair, that we see primitive hair germs, and young papillary hairs of small dimensions, in remarkably wide and long, old follicles. But the greatest difference in the old follicles on bald area regions, compared to the follicles in ordinary casting of the hair, is an *alteration in the direction of the hair*, which Giovannini perhaps overlooked, because, of course, it is not so easily observed on horizontal sections. A great part of the hairless, young, growing follicle is spirally twisted, or bent three or four times in different directions. Then there are found in the upper and central parts of the follicle, dilatations, and between them constrictions, which lead to complete impermeability, and the formation of cysts. I have counted as many as four cysts, with corresponding constrictions, of which the uppermost corresponded to the dilated infundibulum. Many hairs also give the impression of cystically dilated, moniliform follicles, but are really only laterally divided spiral hairs, which have been met in section alternately at different places, laterally or centrally. In these we sometimes see young hairs stretched through the wider parts. But the cysts are always distinctly recognisable, because inside them remains of the old root and young hairs are spirally twisted and often coiled up. These are complete constrictions of the follicle.

These deformities of the empty or insufficiently filled follicles are simply due to the predominance which the muscular power of the skin gets over the follicles, after the disappearance of the resisting stronger hairs. The arrectors sometimes induce bendings, sometimes spiral twistings; the former by bending the under third of the follicle, which has lost its stiffness, from the upper two thirds, the latter by trying to compress the upper two thirds into a lesser space. The dilatations, constrictions and cystic formations develope by concentric, irregular action of the central follicular membrane. Both contractile apparati may be combined in their action, and thus induce still more irregular forms of the follicle.

These deformities of the follicle have further a mechanical action on the young, budding papillary hairs of lesser size, these being bent or compressed, or even rolled up and retained in the follicle. A great part of this after-growth is therefore useless in the replacement of hair, and the down which covers the Area consists mainly only of those

young papillary hairs which have developed under true bed hairs, from the active epithelial processes. The young hairs are also frequently pulled to a side by the over-powerful arrectors, but this does not affect the position of the hair.

The old follicles always show a number of irregular epithelial processes (Harris), often brush-like. These only rarely indicate an increased epithelial growth of the under part of the follicle; they are usually only faintly stained, not rich in chromatin, and owe their development mainly to the circumstance, that in the sudden casting of the hair, a long zone of the follicle with abundant epithelium was exposed, on all sides, to the ensnaring action of the middle follicle membrane, which thus gave origin to irregular constrictions and dilatations of the follicle. But there also appear, at the same place, young buds, rich in chromatin.

While these changes in the follicles attract most attention in the region of Area, there are interesting circulatory phenomena in the still hairy peripheral zone. I can, in this connection, confirm almost all Robinson's statements, and even amplify them, only I have not found his cocci in the lymph vessels, in any of my cases. I found—in contrast to the bald spot—the vessels of the superficial horizontal vascular net, and the oblique arteries and veins, dilated, varying in different places, while the deeper plexus, and the vessels of the hypoderm, were of normal calibre. Since capillary loops of the papillary body proper are scarcely present in the scalp, and the changes which usually take place in the papillary body, are, in the scalp, so to speak, transferred to the middle cutis, this vascular dilatation is not remarkable, being found in most alopecias. The veins of the skin especially are dilated, and I found here, and here only, pretty frequently, the thrombi noted by Robinson. In my preparations they are almost always marginal, leaving a large part of the lumen free. They are formed of red blood corpuscles, enclosing a few or many white ones. These—I have used all known staining methods—show no fibrin and no hyalin. But that they are not simply blood coagula is clear, because they are seated firmly on one side of the venous wall, where the endothelia are absent, or are difficult to stain, and swollen, and because with a good methyl-blue, acid fuchsin, tannin stain, the red blood corpuscles comprising them do not take a dark violet colour, but only a faded, faint rosy stain; their contours are blurred, and finally, the amount of leucocytes in the plug is very varied. These then represent, secondarily washed-out thrombi, partly permeated by leucocytes, and held together by coagulated serum albumen, but not properly fibrinously coagulated. The resistance to circulation could hardly cause them, and I by no means incline, like Robinson, to regard them as the cause of the further changes in the

skin. At least there exists in the first stage, of loosening of the hair, a hyperæmia, localised in the upper and middle cutis, which, on account of the slight affection of the superficial layer, usually escapes clinical observation.

This hyperæmia is accompanied by an œdema distributed through the whole cutis, which is shown, on the one hand, by the dilatation of all the large lymph spaces and vessels, and on the other, by a distinct swelling of the collagenous tissue. In particular, the hair follicles and oblique cutaneous muscles are surrounded by wide lymph spaces; less so the coil glands. Then the œdema is most marked in the upper and middle thirds of the cutis. In sections stained with orcein or acid fuchsin, it is clear that the elementary lymph spaces between the collagenous bundles are not dilated, but that they are rather smaller, from the swelling of these latter, which appear faintly stained in different degrees, and are evidently swollen.

As would be expected, the elastic tissue is displaced, and the coarser threads are somewhat, the finer much less stained than usual. There is a well-marked interstitial and parenchymatous œdema of the cutis.

The Hyperæmia and Œdema are inflammatory, not mechanical in nature. This is shown by the increase of the connective tissue cells around all the dilated blood vessels. These retain the type of spindle cells, and are distinguished by the size of many of their nuclei. There is no question of a general leucocytic exudation around the vessels (Giovannini); even where the thrombi and numerous leucocytes lie directly on the vessel walls, I have only exceptionally been able to note with certainty a white blood corpuscle in the neighbourhood of the vessels. A constant leucocytosis would be a very remarkable phenomenon, where, neither in the cutis, the epidermis, nor in the hair follicles, is there any sign of suppuration. The inflammatory swelling has rather a purely serous character. I can therefore only agree with Robinson and Giovannini in noting the inflammatory character of the primary stage, and if the bald central spot in all cases shows a slight depression, this is due, in addition to the disappearance of the hair, partly to the sodden nature of the surrounding skin.

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Sclerodermia.

Under the name Sclerodermia, we group a series of affections, of circumscribed or general character, which are distinguished by board-like hardness and immobility of the skin. They develope with or without an erythematous-like stage, rapidly or slowly, remain local or gradually extend, with or without a preceding bluish-red zone, disappear slowly, or lead, after long standing, to fibrous atrophy of the skin and subcutaneous tissue, usually with marked development of pigment. We exclude a series of dermato-scleroses, in which the hardening appears only in the last stage, along with atrophy of the skin, as in the marked forms of Perniosis and Raynaud's disease, nerve leprosy, Tabes, and in chronic articular rheumatism, on the skin of the fingers and toes, and varicose legs; and we only admit those forms as Sclerodermia, in which connective tissue hardening is present at the acme of the disease. There thus remains a series of different clinical forms, some of which show anatomical differences. We can distinguish two forms: the *diffuse* and the *circumscribed.*

Diffuse Sclerodermia appears usually in middle age, and gradually, on the upper half of the body, after an erythematous eruption, or myxœdematous-like thickening of the hypoderm, and usually in the form of a diffuse hardening, or of reticular streaks, which afterwards

run together. The main clinical character of all diffuse forms consists in this, that in their extension they are more evident to the finger than to the eye. This depends on the little change in the colour of the skin, which, for long, is yellowish-white, though later more waxy-yellow or dirty greyish-yellow, and gradually passes into the colour of the healthy surroundings; and on the scarcely recognisable change in the level of the skin, which at first is unaltered or only slightly elevated, later, usually somewhat depressed, but never abruptly so. But the perceptible hardening and immobility of the skin is always strikingly marked. Palpation, therefore, is always necessary in the diffuse form. The surface of the skin is unchanged, or, in severe cases, slightly rough and scaly. After some time, there almost always appear pigmented spots, or diffuse pigmentations, sometimes on the board-like parts, sometimes in the surroundings, sometimes quite independently.

Diffuse sclerodermia either possesses, from the commencement, a *universal* character, affecting the whole trunk, a whole arm, the cheeks, the face, the thighs, etc., in progressive symmetrical extension (Besnier's Sclérémie), or it is, for a long time, purely *regional*, limited to the face, hands, neck, etc., without losing its diffuse character, or acquiring a sharp margin. These latter cases may very gradually generalise. Among the most important regional sclerodermiæ are the Sclerodactilæ, with their termination in mutilation, deformity of the bones, etc. Diffuse sclerodermia, both the universal and the regional, always leads to a *striking immobility,* in contrast to the circumscribed, even when that, by its multiplicity, occupies a great part of the body. The joints are semi-flexed, the face becomes a stiff mask, respiration is interfered with, etc. This diminution in the extensility of the skin returns after months or years to the normal, or in more severe cases passes into complete contraction of the affected region, or of the whole body, in the same degree as the initial hypertrophy passes into definite atrophy of the skin.

The circumscribed sclerodermiæ are always striking at a distance, partly by their colour, partly by the different levels of the spots and streaks which compose them; the hardness in many cases resembles that of diffuse Sclerodermia; in others it occupies only a superficial part of the skin, and therefore shows a papery or parchment-like hardness; in others again it affects, preferentially, the deeper parts of the skin, and forms yellowish, transparent swellings and streaks; thus we can distinguish three main forms, which perhaps differ in their nature, but which can certainly be separated histologically. The most frequent is that long known to English authors as *Morphœa;* the second I call the *card-like,** and the third the *keloid-like.*

* Kartenblattähnlich = the paper on which wall maps are mounted.

Morphœa developes singly, or in several, rarely many lesions, slowly and unnoticeably, either directly in its peculiar waxy-yellow colour, as spots from the size of a shilling to that of the palm of the hand, or in irregular or linear form, or in the form of bluish-red spots, with dilated vessels, which gradually become pale from the centre towards the border, where they always retain their bluish colour. The extension of the dull white colour corresponds to the hardening of the areas, which goes through the whole depth of the skin, sometimes even through the hypoderm, to the fascia and the periosteum. More or less pronounced in Morphœa, is a characteristic bluish-red, marginal zone, which shows no hardening, and in the later stages often, between it and the white centre, a border of pigment. Where the spots are thus variegated, the surface has the level of the surrounding skin, and is smooth or covered by fine, dry scales, concentrically arranged. The uniformly coloured morphœa spots are, on the contrary, usually somewhat elevated above the surroundings, and covered with a shiny, stretched horny layer—a difference in appearance which is evidently to be attributed to the greater or less formation of the connective tissue new growth at the surface. After months or years the spots disappear unnoticed, as they came, or they sink in in the centre, and the atrophy of the cutis extends to the deeper-lying tissues, so that deep depressions, grooves and furrows develope, which in time usually heal, leaving behind them a folded, atrophic, usually pigmented skin. Morphœa which appears in round spots, has a preference for the neck, the shoulders, the breast; the linear ones are found—often in Zoster-like arrangement—on the chest, the extremities, the head, here often following the course of the left supraorbital or infraorbital nerve.

The *card-like Sclerodermiæ* appear, like Morphœa, stealthily, as white, much smaller spots, the size of a lentil to a sixpence; they are always sunk below the level of the surrounding skin. There are usually more than one, and they especially affect the breast and the shoulders. The somewhat deepened, bluish-white, mother-of-pearl or chalky-white patches, look as if a visiting card had been inserted in the skin. The spot is now and again sharply marked off from the healthy tissue by a fine, bluish border, and may be raised from the under-lying tissue, thus indicating its position in the upper part of the cutis. This form always heals spontaneously, leaving behind it an area recalling the changes in senile atrophy; it does not attack the deeper tissues.

Keloid-like sclerodermia is the rarest. While the two other circumscribed forms apparently correspond to vascular, or more rarely to nerve territories, are distinctly broader, and show on the surface changes of colour, this appears in the form of coarse cords, sometimes running parallel, sometimes crossing and interlacing, and passing at

their ends into finer fibres; it always corresponds to the lines of tension in the cutis, and evidently to the pre-existing cutaneous bundles. It is of a whitish-yellow colour, less transparent than the normal cutis, and therefore visible in its course. In the centre of each cord, the whole cutis passes into it; it is now and again elevated, in the form of irregularly-margined plates, over the level of the surroundings, and the surface then appears stretched and waxy yellow, as in many spots of Morphœa. As the cords separate and become indistinct at the periphery, they sink more into the depths of the skin. This form is always multiple; I have had under observation a universal, strictly symmetrical case of this circumscribed form, which completely recovered. On account of its branched processes, it has a certain resemblance to spontaneous keloid; it resembles a keloid sinking into the depths of the skin. There is never, here, a lilac border, nor any pigmentation.

Card-like sclerodermia.

Of this form, I have had the opportunity of examining two cases (four pieces of skin), which showed the whole course of the affection. In the recent case, in which the spot appeared on the mamma of an old woman, it had a mother-of-pearl colour and shimmer, a papery resistance, and the size and shape of a somewhat oval lentil. The older spots had lasted for some months, on the shoulders and back of a girl. They were chalky white, somewhat larger than a lentil, very slightly depressed, and had the feeling of a stiff map. This material permitted the study of this remarkable form, up to its acme.

In the early stage, it was seen that the pathological change had affected the papillary body, and an adjacent part of the cutis proper, in the form of a flat patch, which was inserted in the skin, and had a sharp margin. Inside it, all the capillaries as well as the lymph vessels were dilated. In addition, the connective tissue cells were distinctly increased in number, and had a peculiar, unusual arrangement; they were certainly most abundant in the neighbourhood, but not in the *immediate* neighbourhood of the blood vessels, and they did not lead to scattered collections, independent of the blood vessels, here and there in the tissues. At the whole outer border of the patch, laterally and beneath it, these cellular collections were present and voluminous. They consisted of ordinary spindle cells, mixed up with round, very small cells, with deeply-stained, round nuclei, and very little well-stained protoplasm. The cellular collections were loosely formed, and permeated by unusually large lymph spaces. On these places the elastic tissue had completely disappeared, and the collagenous was reduced to fine bundles. In the other parts of the patch, the lymph spaces were also regularly enlarged, and thus all the collagenous

tissue was split up into fine fibrils, and the elastic fibres separated. At this stage, then, neither the collagenous nor the elastic tissue is increased or hypertrophic, the latter indeed is reduced in many places. Nevertheless the patch was thickened beyond the corresponding part of the neighbouring cutis, and this increase in volume is almost entirely to be ascribed to the interstitial œdema, in a very slight degree to the cellular infiltration, for that simply occupies the place of the vanished tissue.

But what is responsible for the sinking of the surface, the mother-of-pearl colour, and the increased resistance? All these questions are answered by a glance at the peculiar behaviour of the epidermis and the sub-epithelial marginal streak. The papillary body at this early stage is almost completely flattened out, only here and there does the epithelium advance in small ridges. This change corresponds exactly to the extension of the patch in the cutis. The prickle layer has been reduced to a thin layer, the granular layer is normal, and the horny layer is much thickened at the expense of the prickle layer. The whole appearance of the epidermis indicates an abnormally great hyperkeratosis, with absence of epithelial after-growth, somewhat as in many cases of Ulerythema centrifugum, and here, as there, the result is a slight depression of the surface; this excessive cornification goes on in spite of the simultaneous œdema of the cutis. But in contrast to Ulerythema centrifugum, the cornification here is regular, and leads to a quite level, transparent callosity. As these circumstances explain the depression and the increased resistance of the card-like sclerodermia, the mother-of-pearl colour is explained by the peculiar conditions of refraction between epithelium and cutis. This margin appears indistinct, even with a low power; with a higher power we see that, instead of regular basal cylinder cells, a series of small, irregular, polygonal epithelia lie on the cutis, and show everywhere between them, coarse, multiform spaces. These spaces are the extensions of dilated tubular lymph spaces, which run through the surface of the cutis in a similar way. There thus developes, over the whole patch, a very irregular, connected system of spaces and tubes, which, inserted between epidermis and cutis, and filled with fluid, must lead to an increased reflection of light, and thus to a milky opacity. The dilated blood vessels, shining through this cloudy marginal zone, give the bluish tinge, while the thickened, smooth, stretched horny layer gives the gloss. Thus arises the resemblance to mother-of-pearl. The spaces of the undermost layers of epithelium extend, here and there, into a coarser or finer inter-cellular system of the upper prickle layer, without leading to a dropsical swelling, or to anything but simple compression of the epithelia.

The spots of the second case represent, on the other hand, the stage of collagenous hypertrophy: sclerosis. The patch has the same arrangement, replacing the papillary body and the upper half of the cutis, but is much more homogeneous. The cellular infiltration has partly disappeared; the larger collections of cells only persist at the periphery, and aid in drawing the line of demarcation from the healthy skin. The vessels, which were dilated in the first stage, are very much narrowed; in many places they have completely disappeared, as have the numerous large lymph spaces. In place of the split-up net of fine collagenous fibres, there is a firm collagenous plate, consisting of horizontal and parallel bundles, which only have very small spaces between them. This progressive change is limited to the collagenous, and does not affect the elastic tissue. The elastic fibres, so far as they have not disappeared in the œdematous stage, are thinned and atrophic, and appear in patches in the collagenous sheath, so that large parts of it appear completely free from elastin. The collagenous tissue also, on some places, is permeated by a network of blood vessels and looser connective tissue, and collections of cells, in which there still appear a few hyperplastic spindle cells, and a very few plasma cells, along with some mast cells, which are never entirely absent.

One of the two spots showed the process somewhat more developed, and thus at its full height. The cellular infiltration has completely disappeared from the collagenous patch, and it is now entirely without vessels; there only remain a few naked nuclei, apparently without protoplasm, between the horizontal bundles, and here and there scattered groups of elastic fibres. But at the border of the patch, there are isolated collections of cells, just as at the commencement, only they appear somewhat better margined. Sometimes they are related to the coil glands or follicles, which margin the patch or run through it in a condition of atrophy; sometimes they are quite independent; they never form a shell round the whole periphery of the patch; they only indicate the marginal line, while in other places healthy tissue passes directly into the patch. In this second stage, the epithelium shows further regressive changes. The prickle layer is reduced to two or three layers, and is perfectly level, while the thickness of the horny layer is still further increased at its expense. The granular layer between still exists, or has disappeared, thus indicating an arrest of further cornification. The epithelio-cutis margin is broken up by the irregularly formed lymph spaces, and is therefore very noticeable. The follicles in the patch are shortened and diminished in all directions, or have completely disappeared, leaving a nucleated cord. The ducts of the coil glands are stretched, and sometimes compressed to thread-like cords, by the

collagenous growth. Only a few of the coils themselves are well preserved, even if they lie under the patch. In the latter case, some are enormously dilated, so that they hardly suggest sweat glands. If they lie at the under margin of the patch, a few of the loops are usually surrounded by cellular infiltration, which affects the lumina in a very irregular manner, sometimes dilating, sometimes narrowing them; the epithelium is partly compressed, partly loosened from the walls; I have not however been able to determine other than mechanical injuries of the coils, in particular no degenerations of the epithelium.

These histological details very well explain the clinical facts. The increased card-like resistance corresponds to the collagenous hypertrophy of the ridge, the deepening, to the epithelial atrophy and flattening of the papillary body, the chalky white colour of the patch, on the one hand to the complete disappearance of the vessels, and on the other to the persistence of a markedly refractile marginal zone. For the disappearance of the vessels, with the persistence of the collagenous tissue alone, would only lead to a waxy yellow, somewhat transparent colour, something like diffuse Sclerodermia, old keloids, the keloid-like circumscribed Sclerodermia, and so on, *i.e.*, the colour of dead, anæmic skin. The *chalky white* change indicates something more, namely marked refraction from a white background.

Morphœa.

Of this form I have only available one typical case. It was that of a young man who, behind the right ear, in the neighbourhood of the mastoid process, had a circumscribed hardness and immobility of the skin, two to three centimetres broad, as far down as the hypoderm. The spots were smooth, yellowish white, were in the level of the surrounding skin, and were surrounded by a bluish white, not hard zone; the excised piece comprised a piece of healthy skin, the marginal zone, and a piece of the board-like centre.

The first important fact was the seat of the alteration in the skin, which extended much further than in card-like sclerodermia, namely, as far as the fatty tissue; the coil glands, consequently, were enclosed in it. It consisted of broad connective tissue bundles, which, in contrast to card-like sclerodermia, crossed in the ordinary way, and showed in their course no important deviation from the normal. This is best seen with an elastin stain, which shows that the elastic tissue is not only normally formed, and has a normal course, but that it is simply separated by the hypertrophying collagenous bundles, and thus forms abnormally wide meshes. The elastin thus does not share in the hyperplasia of the collagen, nor does it disappear.

The thickening of the collagenous bundles has an important but purely mechanical influence on almost all the enclosed structures. The lymph spaces are narrowed beyond recognition, as are most of the lymph vessels, with the exception of some in the upper part of the new formation, which are dilated. All the blood vessels inside the sclerotic part are very much narrowed, the capillaries having often completely disappeared. There is no question of a thickening and hyperplasia of the coats of the vessels, inside the nodule. On the contrary, many of the ascending blood vessels simply appear as endothelium-lined spaces, for the adventitial tissue no longer retains its independence, and has passed into the general collagenous hyperplasia. The loops of the coil glands are separated, by thickening of the connective tissue between them, the lumina are sometimes dilated, sometimes narrowed, usually the latter, and the endothelia are irregularly compressed. The coil glands are usually elongated, and unrolled vertically, by the advancing mass of growth. The hair follicles, too, yielding to the general pressure, are elongated beneath, and diminished in breadth. The papillary body undergoes a special change. It, like the ridge system of the epidermis, is flattened, but not in the same degree as in card-like sclerodermia; the result is a pretty regular wavy line at the border. But the structure is greatly altered. The blood capillaries in some of the better preserved papillæ are narrowed and shortened, but from most they have completely disappeared, having been retracted into the superficial, very much narrowed vascular net. The normally very fine collagenous bundles have become almost as thick as in the upper part of the cutis, so that with a good collagen stain this part does not appear as a delicate, loose net, but as an almost homogeneous, compressed system of bundles. The elastic fibres in the papillary body are preserved, and the lymph spaces are increased in size, but diminished in number. This fact corresponds with the enlargement of some of the lymph spaces and the lymph vessels at the upper cutis margin, and certain lymph spaces in the prickle layer, especially between the basal cells. It is interesting, as a slight analogy to the well-marked dilatation of the lymph spaces at the epithelio-cutis margin in card-like sclerodermia; but in no place does it reach the same development, and thus there is not the same optical phenomenon, the mother-of-pearl or chalky-white colour.

The hyperkeratosis, too, which in that form induces the deepening of the level, is here completely absent. The prickle layer appears to be widened over the sclerotic part; but if one notes the marked flattening of the whole ridge net of the epidermis, this widening is to be regarded only as a transformation of the epithelium into an almost equally thick plate. The granular and horny layers are also normal. Further, in contrast to card-like sclerodermia, the epidermis

in Morphœa participates very little, and purely passively, in the pathological process. In the scaling forms of Morphœa, the epithelium is probably more affected by inter-cellular œdema, and there must be a slight anomaly of cornification, which is here indicated in the slightly dilated inter-epithelial spaces.

All these changes are best seen on comparing the central with the marginal part, where the collagenous hypertrophy is still absent: the vessels have their ordinary calibre, the coils and follicles their normal form, and the papillary body its normal structure. If one compares in the same way the neighbouring zone of the skin, with the sclerotic nodules, in relation to the number of cells, it appears as if there were no difference either in the quantity or in the quality of the cells, but that in the neighbourhood, the connective tissue cells had distinctly multiplied, mainly along the blood vessels, less in the inter-spaces. This multiplication of cells relates solely to the ordinary spindle cells, which are transformed into rows and groups of smaller, rounded cells, with well-stained but small rims of protoplasm. When the collagenous mass appears, these cells, without further multiplying, are pressed asunder, and thus almost all take the form of small spindles. Thus the nodule of Morphœa, in reference to its cellularity, stands mid-way between the cellular and œdematous early stage of card-like sclerodermia, and the very a-cellular acme of that form. That the morphœa nodules also go through a cellular and œdematous stage, I cannot absolutely deny, for I have no such early specimens. But I regard it as very improbable: firstly, because then, in the complete nodules, we would have an irregular distribution of the cells, and here and there larger groups of them, while the distribution is very regular; but mainly, because then the nodules would show an atrophy of the elastic substance, while, as a fact, it is regularly distributed, and normal. Everything seems to point to a proliferation of cells, first around the vessels, and then in the rest of the tissue, and further, to a rapidly developing hypertrophy of the collagenous bundles between them, which separates the cells mechanically, as it does all the other constituents of the skin. That the collagenous new formation arises directly from the cells and their processes, appears to one the more unlikely, the better he is able, by differential staining, to separate collagen and protoplasm. Like the ordinary connective tissue cells, the slightly more numerous mast cells at the margin of the nodule are further separated, but not further multiplied.

But the picture would not be complete without the description of two further points: certain cellular areas at the borders of the nodule, and pigment. At the under and lateral margins of the sclerotic parts, there run certain larger vessels, sometimes cut longitudinally, some-

times transversely, which are evidently displaced by the pressure of the growing tumour, but do not pass into it. The affected veins are very much dilated, and evidently cause the slight bluish shimmer which is seen, clinically, at the periphery. The arteries have a normal calibre and normal vascular walls, but are everywhere accompanied by an adventitial cell growth, which often swells up to thick cellular cords and collections of cells. These collections recall the corresponding ones which are found around the patches of card-like sclerodermia. Here also, the elastin and collagen perish, the former entirely, the latter largely. But in contrast to the cellular areas in that affection, we have here large masses of true plasma cells, and very deeply-stained, smaller cubical cells, with round nuclei and a broad rim of protoplasm. The difference, however, is only gradual; probably the better development of the plasma cells is due to the greater dryness of this form of Sclerodermia.

If we further investigate, on numerous sections, the behaviour of the adventitial layers of the blood vessels, at the side and in the interior of the nodule, we find here only scattered plasma cells in nodules, especially in cell groups, which here and there accompany the coils. Wherever groups of plasma cells lie together, the collagenous tissue disappears, which is in marked contrast to the general hypertrophy of this tissue, seen especially in those sections in which the collagen has been isolated. If sections are digested by trypsin, and then stained, the localities of the plasma cells appear as so many spaces in an otherwise compact tissue.

In one older case of Morphœa, I could better investigate the question of the pigmented border. It was found where clinically we would expect pigment, at the border between the nodule and its surroundings, in the lymph spaces of the papillary body, and in lesser degree in those of the basal prickle layer. It was largely free and in considerable quantity, and was also present, in diminishing degree, over the surface of the nodule. Otherwise, the structure of the nodule was exactly the same as that just described, except that all the changes indicated greater age. The nodule was less cellular, and contained fewer capillaries, the collagenous substance was more homogeneous and still poorer in lymph spaces, and contained elastin as usual; the coil glands and the follicles were still more distorted and diminished. The behaviour of the epidermis and the papillary body was the same, but the extension of the venous blood vessels, at the lateral periphery of the nodules, was still more distinct, the blood capillaries all over were dilated, and the extension of the lymph spaces in the papillary body and at the epithelial margin was much more marked. To this is probably due the very distinct pigmentary deposit on the surface; this

nodule may serve as an example of the multi-coloured form of Morphœa.

Of the regressive stage of Morphœa, I have no specimens, but the conditions may very well be conjectured from what has been said, and from the atrophy of diffuse sclerodermia (*q.v.*), which it clinically resembles.

Sclerodermia diffusa.

I was able to examine a typical case of the diffuse form, at the height of the disease, of three months' standing, in which face, neck, breast, back, arms, and a part of the thigh were affected. Unfortunately I had not the opportunity of studying the first (mainly erythematous) stage, which is the more important in this form, since we cannot, as in circumscribed Sclerodermia, draw conclusions from the marginal parts. But four pieces, excised at different periods, gave a pretty distinct view of the process ; it is evidently simpler than that in the circumscribed forms.

The main process is a hypertrophy of the pre-existing collagenous bundles, which affects equally all parts of the cutis, and leads to simple pressure atrophy of the vessels, as well as of the epidermic structures. In the piece first excised, the blood vessels running through the thickened cutis, and those of the superficial net, were still dilated, and surrounded by swollen and moderately multiplied connective tissue cells; but the structure was otherwise not altered. In later pieces, with increasing collagenous hypertrophy, the vessels were strikingly narrowed, cord-like, and often distorted by the compression of the crossing connective tissue bundles. The spindle cells, which at first were abundant in the cutis, became more sparing and smaller ; they were at first preserved in the immediate neighbourhood of the vessels, and in the papillary body, but gradually disappeared, all but their nuclei, and a very small rim of protoplasm with hair-like processes. Since the connective tissue of the papillæ goes through the same transformation, their form becomes plumper. They increase, especially in breadth, and compress the ridges of the epidermis between them, down to a few layers of the epithelium. The supra-papillary prickle layer is thickened a little. But except for these mechanical changes, there is no affection of the epithelium. The dilatation of the marginal lymphatics, so characteristic of Sclerodermia, and less so of Morphœa, is altogether absent, or only suggested. The lymph spaces through the whole cutis are narrowed, and—corresponding to the homogenised character of the cutis—in many places more circular, dug out in the collagenous substance, more like narrow canals than the ordinary spaces and multiform cavities.

The hair follicles are diminished and shortened during the process,

as the result of the general increased pressure, without any independent changes having taken place in the follicle apparatus. The coil glands in all preparations are closely surrounded by the collagenous mass, partly narrowed and partly dilated, almost always displaced, but not otherwise altered. The inter-tubular tissue does not appear to be affected in the process, as it sometimes is in circumscribed Sclerodermia.

More interesting, though only passive changes, are seen in the elastic tissue. At the commencement it is simply pressed asunder by the swelling collagenous bundles, but retains, in general, its arrangement. Later on, it yields in many places, atrophies, and there appear irregular tensions, which lead to larger spaces, alternating with other spots in which the elastic fibres are collected in bundles (Schadewald). The chaotic arrangement at these places shows that it is not a new formation of elastic tissue. Other authors have described a multiplication of the elastin (Wolters). Further, there are frequently found in the neighbourhood, elastic spheres and collections of them, sometimes of astonishing size, which also indicate the disappearance of elastic substance. The single exception to the general pressure atrophy are the muscles, which, though not actually hypertrophic (Rossbach, Dinkler), as they here and there seem, are by no means atrophic. We see that the tension of the elastic tissue by the swelling collagenous substance is able to induce a reactive activity of the cutaneous muscles.

The fatty tissue also disappears, and is replaced by collagenous tissue. My sections, although going much deeper than the coil glands, show no trace of it. But I am unable to say, whether at the under margin—as in the circumscribed sclerodermiæ—peculiar cell areas are present or not. Probably not, for there is no suggestion of them inside the cutis; but this point must remain for future investigation.

Histologically, then, we have every reason for regarding diffuse Sclerodermia as a much simpler process than the circumscribed; only the collagenous hypertrophy is common to both.

The ultimate atrophy of the skin after long persistent, diffuse hypertrophy, does not importantly differ from general atrophy from other causes. It is sometimes brought about here, too, by an obliterating endarteritis. At first the disappearance is evident in the epidermic structures and vessels, while the collagenous tissue only later diminishes. The ultimate result is a parchment-like, thin cutaneous plate, without suggestion of hypoderm or papillary body, and covered by atrophic epidermis.

A review of these forms of Sclerodermia shows that the histological investigations correspond to the clinical, and that a uniform view of Sclerodermia is no more supported anatomically, than clinically and prognostically. The common link which combines them all is the

hypertrophy of the collagenous tissue, while the inflammatory appearances, indicated by cellular growth and dilatation of the vessels, are different in form and degree in each. I do not therefore share the view recently put forward by Dinkler, that an affection of the vessels is the most important change in Sclerodermia, and that a specific arteritis is essential.

Dinkler, like Lagrange, has shown that the nerve centres and peripheral nerves in this affection are free from pathological changes, as are the heart and the large vessels. He was the first to study thoroughly the vessel changes which were seen by Rasmussen and Neumann. It is therefore necessary, in conclusion, to consider somewhat more closely the grounds on which he bases this view, one of significance in many dermatoses.

Dinkler finds cellular growth on the adventitia and media of the arteries, disappearance of the elastic tissue of the media, and finally, an obliterative growth proceeding from the media and intima, with closure of the vessels, and thrombosis. He regards this as primary, because it appears contemporaneously, or earlier than the "cutaneous changes." The specific cutaneous change consists in a collagenous hypertrophy. On the arteries of the skin, this is only evident in the obliterative intima growth towards the conclusion, and it appears much later than the collagenous hypertrophy of the cutis. The latter rather coincides with a cellular growth around the vessels. Were the vessel disease the essential of the process, there must be a preceding sclerosis of the vessels, as in the syphilitic initial sclerosis; we would see, at a certain stage, sclerotic vessels running in the normal cutaneous tissue, which we do not. The cellular growth on the vessels, and the hypertrophy of the collagenous tissue, are the simultaneous results of the same, as yet unknown cause, and the latter change alone is characteristic of this process.

Then the obliterating arteritis, as Dinkler himself admits, is limited to certain of the supplying arteries; some, and in my preparations many, do not undergo this change. This is very much against any necessary relation of vascular obliteration to diffuse cutaneous change, and the drawings given by Dinkler in no way differ from those of other dermatoses where there is arteritis obliterans * and in which there is no sclerodermatic character of the skin. Therefore the arterial obliteration and thrombosis by no means explain the occlusion of the capillaries in sclerodermia, as Dinkler would have it; they are much too late, and not complete enough. Capillary occlusion is rather one of the results of the collagenous hypertrophy. But it is quite incom-

* The disappearance of the elastin of the media, the elastic lamella, and the passage of the media into the intimal growth, are usually found in Arteritis obliterans.

prehensible why Dinkler attributes the dilatation of the veins to the diminished flow of blood through the narrowed capillary region. That could only have the effect of narrowing wide veins. The venous stasis and venous dilatation at the periphery of the affection are not a necessary, though a frequent sign of over-filling of the collaterals adjoining the occluded region, and their existence indicates a free flow of blood to the sclerodermatic part.

To the same conclusion, *i.e.*, that the arteries are not affected before the rest of the skin, another fact mentioned by Dinkler points, namely, that they are affected from without inwards, that peri- and mesoarteritis preceded the endarteritis. And to me the immunity of the heart and the larger vessels in diffuse universal Sclerodermia is hardly compatible with the assumption of a general peripheral vascular disease, leading to arterial obliteration.*

In summing up, I can consequently not see, in this arteritis, which now and again goes on to obliteration, anything characteristic of the process, or capable of explaining it; it certainly does not explain the important appearance, the *hypertrophy of the collagenous intercellular substance.* The ultimate obliteration of certain arteries I would rather regard as the independent result of the capillary occlusion, induced by sclerosis of the cutis.

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* Dinkler's view is evidently partly supported by the fact, that the author regards his Case 3, which was a typical regional case of multiple Morphœa, on account of the ultimate union of the spots, as one of the totally different form of diffuse sclerodermia (Sclérémie Besnier), and thus establishes an unfounded proof of a transition between the two forms.

Thus Dinkler comes to the incorrect conclusion, that in Sclerodermia there is always a previous hyperplastic stage, with increase in volume and *without increase in consistence;* in diffuse Sclerodermia, this latter is practically present from the commencement. Thus we explain the absence of sweating in Case 3; while in diffuse Sclerodermia sweating always persists, and is sometimes increased.

Ainhum.

A not uncommon local affection of the little toe, which occurs in negroes in Africa and South America, in which the toe is gradually snared off from the rest of the foot, by a deep furrow.

In this disease we have the very interesting occurrence of a primary degeneration of the skin, a sort of ring-formed Sclerodermia, with callous formation of the epidermis, which by its seat at the base of a limb leads to a secondary, total stagnatory necrosis, which has a close resemblance to the artificial, elastic snaring of tumours. In spite of numerous histological investigations, the nature of the whole process is still unexplained, largely because it is not clear from the descriptions, which changes are primary, and which secondary. In future, for the establishment of the nature of the primary sclerotic process at the base of the toe, it would be necessary to examine an earlier stage than has previously been done.

All agree that in addition to chronic inflammation, there is a marked hypertrophy of the epidermis. The horny layer is very much thickened, as is the ridge net of the epidermis, and the papillæ are consequently elongated and narrowed. The basal prickle layer is, as is usual in negroes, deeply pigmented. In the papillary body, there is a cellular infiltration. The papillary vessels are dilated, and the larger and deeper lying vessels of the cutis and the hypoderm show obliterative endarteritis, in different stages of development. But while Wile found the coil glands atrophic, Eyles afterwards found growth of the glandular epithelium, with thickening of the membrana propria. Since such progressive changes are constantly found in stagnatory dermatoses, in the neighbourhood of varices, &c., their occurrence in Ainhum is nothing unusual. Wile found a loosening, and inflammatory œdema of the hypoderm; Eyles, on the contrary, a fibrous hypertrophy.

In future investigation, the commencement of the affection must be examined; and where only the terminal stage is present, the primary process at the furrow, and the secondary degeneration of the distal parts must be separated, if we are to learn anything of the influence of the former on the latter. Then we will learn whether the affection shows primary appearances of inflammation, which, from the clinical history, is improbable, for the snaring takes place painlessly, and without any appearances of dermatitis. Perhaps the microscopic symptoms of inflammation are related only to the traumata which appear in the last stage, and which often induce ulceration, partial necrosis and severe pain. The distension of the ensnared toe appears to indicate a stagnation of lymph and fat, which gradually leads to degeneration of

all the constituents of the cutis, and then to a rarefaction of the bones, the total disappearance of the ungual phalanx, the partial disappearance of the second, while the third is almost always preserved. Whether the ensnaring ring is due to a callous formation, as in perforating ulcer, or to a sclerosis of the cutis, has not yet been explained.

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Section V.

MALFORMATIONS.

It is by no means easy to separate, off-hand, the directly congenital growths of the skin, from the group of the benign tumours. Several of the former are at birth invisible, or scarcely visible, develope slowly with the advancing development of the whole body, and yet they undeniably indicate an anomaly of the skin, present at birth. Such are especially the nævi, in the stricter sense, and also almost all cases of so-called Elephantiasis congenita (fibromatosa, lymphangiectodes, angiomatosa), the dermoids, atheromata, etc. In many of these cases, the existence of the tumour may be traced to birth, or to the first year of life. And these in no way differ from the cases in which the growth is first noted after puberty, or even in adult life. Among the latter cases, there are found instructive examples of heredity, of these, or of similar tumours, in certain families.

Esmarch and Kulenkampff have collected a formidable series of such genealogical tables, in connection with Elephantiasis. But even daily observation shows a perfectly apparent heredity of ordinary mother's marks, which often appear in ascendants and descendants in exactly the same regions of skin, and are often strikingly similar.

The congenital idea must therefore be widened, so as to include not only the visible and palpable tumours, but also an invisible and impalpable sub-stratum, which assumes active growth, sometimes in utero, often directly after birth, but most frequently in different later periods of life (puberty, climacterium, old age). This development may occur either suddenly, or, again, very gradually, and without reference to any particular period.

This latent excess of tissue may be regarded in two different ways, viz. either as actual elements, ensnared during some period of embryonic development, without relation to the surrounding tissues or to the remaining utilised elements, which have preserved, with the form of embryonic cells, their intense activity of production, and ought to be recognised histologically as such. Or it may be that there is virtual excess in productive activity, without any material, recognisable sub-stratum, common to certain cell territories, and without any aberrant,

unutilised germs from the embryonic period being microscopically demonstrable.

Of course, the first view, which forms the basis of Cohnheim's theory of tumours, is more satisfactory ; it can always be supported by the discovery of histological facts ; indeed, in dealing with congenital tumours, we must, where possible, demonstrate a real, visible germ. But we have abundance of proof, that this, in certain cases, is not possible (as in the hard nævi) ; and we must in those cases, and in others in which as yet no excessive embryonic constituents are to be found, for the present be content with the less satisfactory assumption that certain parts of the tissue, without having suffered an arrest in development, show an excess of productive power—a power of assimilation and division—which enables them to develope enormously.

From what has been said, it is clear that, in this chapter on the congenital tumours, in addition to many strictly congenital, we shall meet others which can only have a congenital basis (real or virtual). The reasons why some are placed in this chapter are, either the actual recognition of embryonic, unused germs as the basis of the tumour (soft nævi), or the identity of their structure with strictly congenital forms, or finally, the clinical recognition of an hereditary basis. In many cases, several of these reasons are present ; and then the structures are always recognised as congenital or nævus-like. The difficulty of classification lies less in the admitted doubt of their relationship to these forms, than in the circumstance, that for a whole series of other tumours, previously reckoned with the acquired benign growths, the recognition of their congenital nature coincides with the wider sense here mentioned. In any case, the by no means unimportant class of congenital malformations of the skin is certain to increase at the cost of the benign tumours.

A.—Progressive Disturbances of Nutrition.

1. Proliferative Growths.

(a). *Syringadenoma* (*Syringoma*).

The adenomata of the coil-ducts more frequently form independent tumours than those of the coils. This difference is probably due to a physiological difference between the two. In the coils there are normally found fewer mitoses than in the ducts. The former represent highly differentiated epithelium, adapted to a very complicated end ; the latter, almost unchanged surface epithelium,

which, as the spiral form of the duct epithelium even in the horny layer shows, is continually proliferating. If this be considered, it is not remarkable that the coil-ducts also share in the peculiarity of the surface epithelium, and send solid epithelial processes into the cutis, while this property has been almost altogether lost by the coils.

In this tendency to constant proliferation from a simple irritant, and in the absence of a higher physiological function and anatomical structure, the ducts of the coils of adults resemble still undifferentiated processes in the embryo. One may therefore very well combine them as simple tubes (Syrinx = narrow duct), as opposed to the complete

FIG. 37.—Syringadenoma. Showing canals and cysts, with varied contents.

S. Solid processes. *C.* Cysts containing hyalin masses. *D.* Cysts containing degenerating epithelia. *H.* Horny cysts.

coil (Spira). As a fact, the tumours which proceed from the developing coils resemble those tumours of adults which arise from the ducts of the coil glands. And both are very different in their structure from the true Spiradenomata. In many such tumours, it has not been possible for investigators to find any important difference between the protuberances of the complete ducts, and the embryonic foundation of a coil; while as yet there has never been found a transition of an

adenoma of the duct into one of the coils. It further serves to distinguish the Spiroma from the Syringoma, that the former only appears in adults, and indicates an acquired change; while syringoma has a congenital character, even if it only attains later, its full development.

The first description we owe to Jacquet and Darier, who described it under the names: "Hydradénomes éruptifs," then as "Epithéliomes adénoides des glandes sudoripares," or shortly as "Adénomes sudoripares." The histogenesis was then explained in a work by Török, under the simple name — Syringadenoma; or on account of the accompanying cyst formation—Syringo-Cystadenoma. I prefer the simple expression Syringadenoma * for this growth, for the formation of cysts with hyalin contents, is common to all Syringadenomata, therefore unnecessary in the nomenclature.

> The affection appears in adults, in the form of peppercorn to pea-sized, indolent tumours, spread in pretty regular symmetrical distribution on the surface of the trunk, especially on the upper part, underneath the clavicle; and it extends in diminishing degree on the anterior and lateral parts of the chest, while it reaches but little from here to the anterior part of the neck and the inner surfaces of the extremities. Still more rarely are there found a few tumours on the eyelids or on other parts of the head. This topographical peculiarity is important, for the allied, but histologically very different Acanthoma adenoides cysticum has its seat of predilection in the centre of the face. The tumours are at first the colour of the skin, but later, become somewhat dark, reddish or bluish. They are not particularly striking, and remain at the stage of bean-sized, slightly elevated nodules. They do not possess the striking, clear yellowish colour, and the black points of Acanthoma adenoides cysticum.

In the central, partly hyperæmic parts of the cutis, we find smaller or larger cysts; and also straight or winding, small, solid processes of epithelium, some of which on every section are seen to be connected with one or two cysts. The cylindrical epithelial processes have about the thickness of ordinary coil ducts. They are rarely smaller, but are often markedly dilated, and then have a sort of lumen and contents. The cross sections of these cylindrical tubes are not always easy to separate from the spherical or oval cysts, as both may contain hyalin, or cast-off epithelial masses. Neither epithelial cylinders, canals nor cysts have a true Membrana Propria. The latter two are clothed by two or three layers of flat epithelia, which towards the lumen swell up, undergo hyalin degeneration, and become a homogeneous or cellular mass, which forms the contents of the wider canals and cysts. We find all transitions from thickened parts of the cylindrical canals, which are simply distended by the accumulation of epithelia inside them, to

* Syringoma is still shorter and equally clear, for the word syrinx as described above, relates only to embryonic glands or portions of glands in adults.

smaller cysts, which have formed from the hyalin degeneration of these epithelia, and to larger cysts, which are very much dilated by the stagnating layers of degenerated epithelium. The epithelial cylinders which often unite two closely lying cysts, are, with their increase, thinned, and finally torn; by this process of punctiform proliferation and degeneration, there may develope from a solid epithelial cylinder, several epithelial cysts, lying isolated in the cutis.

Török could not recognise any sign of budding in the well-preserved coil ducts, and no connection with the epithelial cylinders and cysts, nor with the well-preserved, deeper lying coils. In this, his observations agree in the main with those of Darier. But while the latter is nevertheless inclined to ascribe the peculiar epithelial formations to the coil glands, Török legitimately concludes that they do not develope from mature coil ducts, but from embryonic foundations of coils, and represent "aberrant coil germs." This explanation, which corresponds with Cohnheim's theory, would involve the conclusion, that during embryonic life, solid epithelial buds which had entered into the cutis had been snared off from the surface, had lived for a long time inactive in the cutis, and then, at a later epoch of life, somehow led to the formation of benign tumours. This development is indicated on the one hand by the small number of coils and ducts in this region; and on the other by the fact that isolated cysts are found among the cutaneous muscles, and between the lobules of the sebaceous glands, where they could only be if those normal organs were growing round the aberrant germs. This latter fact indeed indicates the very early snaring off of the developing coils. I adopt altogether this view of Török, especially as the whole clinical behaviour of these tumours shows them to be a form of Nævus.

L. Philippson found later, in another case, in my clinic, that, in addition to the cysts with hyalin contents, there were others filled with horny cells. From this we must conclude that, in addition to the germs snared off very early from the surface epithelium, similar snarings take place at a later fœtal period, when true kerato-hyalin cornification is going on on the surface. It is only natural that cysts developing from such epithelial germs should show kerato-hyalin, and produce horn. This view is further supported by the fact, which Philippson has noted without having explained it, that these horny cysts are only sub-epithelial—only towards the surface; this also is a result of their later snaring off.* When, however, Philippson, on account of the horny cysts, regards the whole tumour as one snared off

* For the later snaring off in Philippson's case, there is further his observation of incompletely developed, but quite recognisable, developing coils (blind ducts, duct-like epithelial processes).

from the surface epithelium, without any special, even if erroneous object, and therefore calls it " benign epithelioma," I cannot admit his conclusion. For it is clearly distinguished, by its formation in the coil type, from all other nævi in which large quantities of really undifferentiated surface epithelium slumber. For the same reason, Philippson's view of colloid milium, and its comparison with ordinary milium as being both varieties of *one* form of tumour, is not acceptable. If I had diagnosed colloid milium in a case of a transparent, hard, yellowish nodule of the eyelid, such as he described, from having seen some of Baretta's casts, the diagnosis would have been abandoned as soon as it was clear that the tumour was a Syringoma : for this form of tumour is now pretty well known, while no one knows exactly what the old casts, called Colloid milium, in Baretta's museum, really are.*

When Philippson further identifies Besnier's " Colloid degeneration of the cutis " with his Colloid milium, this attempt to simplify our knowledge is in vain, since we have in recent French works become better acquainted with colloid degeneration of the skin (*q.v.*). Unfortunately, Philippson's observations of scattered Syringomata of the eyelid have, among other reasons, led Brooke to classify typical hereditary acanthoma, as observed by Perry and himself, occurring mainly in the face, with the Syringoma, because " the structures may occur in any part of the body." It is high time that an end was made to this confusion. There are among the Nævi not many affections which are clinically and anatomically so distinct as those described by Jacquet and Darier on the one hand, and by Perry and Brooke on the other.

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(b). *Acanthoma adenoides cysticum.*

An affection which has as yet only been observed in England and America, consisting in the appearance of pin-head to pea-sized, shining, somewhat transparent nodules, at first the colour of the skin, later becoming pale yellow or pale blue, and some of them containing white, milium-like insertions. They prefer so remarkably the region of the eyebrows, the root and alæ of the nose, the adjacent parts of the cheeks, and the surroundings of the mouth, that all the cases known resemble one another. The anterior upper side of the trunk, a favourite seat of Syringoma, is in this case almost free. A few growths are found on the back, more on the neck, and very numerous large ones on the hairy scalp. Brooke observed three cases in one family ; Fordyce, two.

* Possibly some of them are the Acanthoma adenoides cysticum of Perry and Brooke.

This interesting form of tumour is, through the careful investigations of Brooke, Fordyce, and Balzer, almost as familiar in its structure as the Syringoma, which is sometimes confused with it. It is composed of solid (never tubular) epithelial processes, evidently derived from the surface epithelium, or from the prickle layer of smaller lanugo hair follicles, which grow in the cutis, in the form of fine, finger-like processes, glandular protuberances, net-like or lattice-like, or completely solid, coarse masses, and, displacing the normal constituents, affect all parts of it, from the fat lobules to the surface epithelium. The Syringoma, on the other hand, tends to tubular form, is long independent of the surface epithelium, has never any connection with the hair follicles, never shows lobulated or branched masses, but always the duct form; or it forms isolated cysts, induces no displacing pressure on the normal elements of the cutis, and is restricted to the central parts.

Brooke further recognised that the epithelial masses were always

FIG. 38.—Acanthoma adenoides cysticum (Brooke).

A. Epithelial tract. *B*. Small cyst. *C*. Masses of epithelial new growth, showing convoluted tracts.
D. "Capsule" of connective tissue. *E*. Two finger-like epithelial growths, arising from a hair sack.
F. New growth proceeding from the solution of a hair sack. *G*. Cyst lined with concentric horny layers.

defined on the outer side by cylindrical cells, and that in many places this palisade-like epithelial margin also showed a distinct basement membrane. But he always found the epithelial processes encapsuled by a highly cellular connective tissue, with numerous leucocytes, especially in the youngest tumours. The constant palisade form of the

peripheral epithelia, as well as the firm connection of these epithelia in general, even in their finest reticular structure, indicates, though Brooke and Fordyce do not note it, a developed system of epithelial fibrillation. The Syringoma shows neither this constant peripheral cylinder-cell layer, nor a limiting membrane; we never find the epithelial cylinders of Syringoma encapsuled by a special connective tissue sheath, and there is no epithelial fibrillation, or prickles in the cells. If the presence of the latter is confirmed in Acanthoma cysticum, this alone would suffice to distinguish the tumour from Syringoma, and would point to a much later development.

The only thing analogous in both tumours, is the formation of colloid or hyalin cysts. Brooke never found horny pearls alone, but he did find hyalin pearls surrounded by cornified cells. In this also, the two tumours radically differ. In Syringoma, whole segments of the thin epithelial cylinders are converted into cysts, which enlarge, and are snared off, so that they are quite isolated. In Acanthoma cysticum, the cysts of varied size are scattered all over the new formation, and are always surrounded by epithelial masses.

The histological appearances of the two forms of tumour consequently differ as much as the clinical, and there is really scarcely any reason for the confusion of two affections so well characterised. Hyalin degeneration and cystic formation are such widespread epithelial changes, that they alone certainly do not justify such a classification. As a fact, the error arose because Jacquet and Darier described their tumour as Hydradenoma, and Perry his, somewhat boldly, as Adenoma of the sweat glands; neither of them correctly. The tumour under consideration is a pure Acanthoma, which is distinguished by its tendency to cystic formation. The name Acanthoma is the more suitable, inasmuch as we are probably dealing with a growth of true prickle cells, of a later fœtal period; and if Brooke and others desire to re-introduce the name "epithelioma," without the troublesome adjective "benign," for non-malignant growths of the surface epithelium, I would advise that it be reserved for those growths in which no prickles and no epithelial fibrillation are present. Where these are found, the difference in their structure is clearly defined, and they already possess a better appellation, namely "Acanthoma." Moreover, I accept Brooke's nomenclature in regard to the adjective "adenoides," for it makes it quite clear that we are dealing, not with the commencement of glands, but only with an external resemblance to glands—Acanthoma adenoides cysticum.

To the cases of Perry, Brooke, and Fordyce, we must add one older case, although this has previously been regarded as an example of Adenoma of the sebaceous glands; it is at the same time the only one yet described in France.

The case of Balzer and Ménétrier was that of a girl of 21, whose mother was said to have suffered from a similar affection. With the appearance of menstruation, there appeared firm, small, indolent nodules, as large as a pin-head, or a pea. These were of the colour of the skin, embedded in it, projecting semispherically or somewhat more pointedly, and never running together, however closely they might be packed. In many of them, were small, white, milium-looking points. They appeared first on the forehead, and gradually extended over the face, scalp, neck and ears. They were densest over the frontal protuberances, all around the nose, especially in the nasal, labial and labio-mental furrows.

Microscopical investigation showed that the tumours consisted of epithelial masses, which lay scattered in the connective tissue of the skin, in the form of lobulated nests, and which contained cysts in their interior. These cysts were sharply circumscribed, and extraordinarily variable in form; their branching resembled very much that of the lobules of the tubular or acinous glands; and the suspicion that they partly arose from sebaceous glands became a certainty, by the recognition of remains of sebaceous glands, with which they were in direct connection. But this observation was exceptional. Most of the growths were absolutely irregular, and were, by reason of their size, removed some distance from the originally superficial seat of the sebaceous glands. The everywhere recurring main form was that of thin, solid, cylindrical, reticular epithelial processes, similar to those of reticular carcinoma. In addition to the sebaceous glands, the hair follicles and some of the sweat ducts also contributed to the growth, while a coil apparently did the same. In some places, too, the surface epithelium seemed to pass directly into the tumour, while in general it was unaffected. Very numerous cysts were seen all through the epithelial nests, thirty or more in one section. The cysts were conspicuous with a picro-carmin stain, by their yellow colour, had a leaf-like arrangement, and were formed of fatty substance. The authors regard them as a transformation "en éléments sébacés." How, in their alcohol preparations, they were able to recognise these sebaceous elements, and whether they really had the structure of sebaceous cells, is not said; but their figure (3) shows distinctly that they were not sebaceous cells, but hyalin or colloid fragments. All the epithelial nests were sheathed by a sort of connective tissue capsule, which in the younger nests was more highly cellular than in the older. The epithelia which constituted them, resembled the non-fatty, young sebaceous cells, and stained dark red with picro-carmin. The greater number of the cysts contained no fat, and consisted of flattened horny lamellæ; they differed from ordinary horny pearls, by the irregular arrangement and want of nuclei in the innermost cells. Some cysts were simply hair-containing retention cysts.

As Chambard, in reviewing this work in the Annales, says, there is no proof that the growth is really an Adenoma of the sebaceous glands; and he correctly describes it as a metatypical tubular epithelioma. Since Brooke's description has made us familiar with Acanthoma adenoides cysticum, there is no doubt, that in the so-called Adenoma of the sebaceous glands, of Balzer and Ménétrier, we have the same affection. From the clinical history down to the finest histological details, it agrees exactly with the cases of Brooke and Fordyce, and I have given it so fully that the reader himself may make the instructive comparison.

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(c). *Keratoma palmare et plantare hereditarium.*

A typical, hereditary, isolated thickening of the horny layer of the palms and soles, occurring in several generations. In the cases under my observation, there was seen, in infancy, in the neighbourhood of the flat keratoma, a bluish halo, which afterwards disappeared. In the case of a second family, there was no superficial or deep marginal hyperæmia, but in Thost's case there was a reddish marginal rim. There was always more or less hyperidrosis of the affected surfaces; touch was normal, but the perception of heat and pain was diminished, as in callosities.

The only histological investigation is that of Thost. He found the papillæ very much elongated, as much as five times their original length, and the prickle layer correspondingly very much thickened. The granular layer was widened, but the basal layer remained normal, and was not so well marked off from the rest of the horny layer as usual. Most of the thickening of the horny layer was in the middle layer. The cutis and the fatty tissue were also thickened, and the blood vessels wider than normal. The coil glands were especially enlarged, almost twice their normal size, the ducts less hypertrophic; the sweat pores, with their conical openings in the horny and granular layers, were particularly large and distinct.

The thickening of the cutis and the fatty tissue, as well as the very marked acanthosis and hypertrophy of the coils, which Thost found, stamp this congenital tumour formation as a nævoid hypertrophy of the whole palms and soles. At all events, in his cases, it was not a simple keratoma, as the extension of the skin of the sole on the back of the foot and toes, and the reddish margin, show. My case appeared to be a pure keratoma, and perhaps some distinction is

necessary. Until further investigations have been made, I have thought it desirable, in spite of the name, to rank the affection among the proliferating tumours.

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(d). *Verruca dorsi manus et pedis.*

This peculiar form of tumour, which is by no means rare, I recognised several years ago, under the above provisional name. The tumours are usually regarded by their owners as a sort of ordinary wart, possibly because they are described by many as Verrucæ; but they have nothing to do with seborrhœic warts. It is essentially a *systematised hard nævus*, which always appears symmetrically, in groups, and whose main peculiarity consists in its sharp limitation to the region of the metacarpi of the thumb and index finger on the back of the hand, and the corresponding region on the back of the foot. In one case it was hereditary. The warty-like protuberances are quite flat, round or polygonal, two to six millimetres in diameter, finally punctate on the surface, and appear in middle or later life; they do not, like Verruca vulgaris, further increase or completely disappear.

I had the opportunity of examining a group of these nævi from the back of the foot. The cutis underneath the thickened epidermis is here completely normal, and even the slight appearances of irritation which occur in older verrucæ, are absent. The epidermic growth is distinguished at the first glance from that of verruca, by its perfect regularity. The prickle layer gradually thickens from the border to the centre, where it has about the thickness of that of the sole of the foot. In a quite analogous way, the granular and horny layers are thickened. We see an appearance of gradual epidermic increase, similar to that at the border of the foot, as we advance from the back of the foot towards the sole, especially as all the layers are otherwise normal. The deeply penetrating epithelial ridges, with their displacement towards the centre, their irregular cornification, the partial flattening of the papillæ, and the bursting of the horny layer—all these symptoms, and others which characterise Verruca, are here absent; and thus, neither histologically nor clinically, are we dealing with a modification of the ordinary wart. In any definite arrangement of the group of systematised nævi, this form must be borne in mind.

(e). *Nævi.*

The subject of Nævus maternus—mother's marks—has, in distinction to most of the conditions treated in this book, made its way from

popular to scientific cognizance, and therefore its adoption has met with great difficulty. Originally, the term was applied to circumscribed anomalies of the skin, striking from their colour, which, as they do not alter like the ordinary skin diseases, serve as distinguishing marks. Their development was not only considered as dependent on hereditary circumstances, but was also the subject of all sorts of superstitions. Since heredity has become of importance in many anomalies of the skin, and the more important, as its domain is, on account of the discovery of innumerable infectious diseases, daily diminished, and since the striking, easily examined mother's mark, whose heredity is so easily proved, forms a most appropriate foundation for a future theory of heredity, we cannot very well dispense with a scientific conception of the nævi. We must, therefore, be satisfied with sharply defining them, so that at least they may not be a source of error.

If, bearing in mind that possibly most benign tumours of the skin are to be attributed to congenital disturbances of growth, or aberrant embryonic germs, the definition of nævi were to be identified with that of the benign tumours, we should only open an interminable conflict between theory and practice. On the other hand—in the course of a study of the fibro-keratomata, which casually included that of the nævi also—I regarded it for a time as possible to replace the definition of nævus by a number of individual, purely anatomical definitions. But this very study drove me from this explanation; for I found that all these new formations went through a *peculiar history of development,* whose first and last phases were often so far apart, that a simple pathologico-anatomical arrangement of the nomenclature is absolutely impossible. Thus the soft nævi begin as epithelial growths, and often end in simple œdematous connective-tissue tumours; the fibro-keratoma begins as a fibroma nodule, and ends as a simple keratoma. And if, in the latter case, a short and precise relation is possible, this would not be possible everywhere; and the object of achieving a simple classification of all these divergent conditions, on a purely anatomical basis, would have been impossible to attain.

We are consequently driven, since we can neither do without it, nor replace it, to adopt the definition of nævus as used by the laity, and only to give it a stricter signification. Popularly, all universal changes of the skin, of a congenital nature, are not called nævus. Neither the congenital universal changes of the skin, nor the striking peculiarities of the hairy men or Albinos, are so indicated. The definition is limited to circumscribed cutaneous anomalies. More careful investigation has however shown, that certain widespread anomalies of pigment and hair, which sometimes occupy the greater

part of the body, are anatomically just the same as the small nævi of the same nature. We must consequently scientifically place them with nævi, although this is against the popular view; I would describe them as giant nævi.

We follow the popular view in excluding new formations, *of the colour of the skin*—the palmar keratoma, congenital lymphangiomata, subcutaneous dermoid, atheroma, etc.—from the nævus group. Further, it does not correspond to the popular view to describe as nævi those circumscribed new formations which gradually take on *collossal dimensions.* Here we meet with the vague and purely external ideas of elephantiasis. Finally, those congenital, circumscribed malformations, in which there is only a defect in colour or of the whole skin, are hardly to be regarded as Nævi. After removal of all these, the nævus group is far from being a perfectly clear, complete one; in particular, the position of the Nævi lineares is very problematic. For, if the popular view of the unchanging conditions of all nævi must in our sense be so limited, that we admit, on the contrary, that nævi go through a special development, but so gradually that the changes are insensible to casual observation, on the other hand, the nævi lineares are distinguished by their very rapid development during extra-uterine life. It is therefore questionable whether this definition of nævus can be retained in the long run.

Positively, the group of nævi comprises, after this elimination, the soft or hard, small, wart-like tumours, with or without pigment, the simple, similarly-formed hypertrophies of pigment, the circumscribed hypertrophies of hair on otherwise hairless places, and the congenital venous angiomata. These all come into the following definition, which may serve to characterise the group of nævi: *circumscribed, small malformations of the skin, which have a hereditary basis, or have their foundations laid in embryonic life, become evident at different periods of life, develope very slowly, and are distinguished by their colour, or the form of their surface.*

We might remove, as an anatomically well-defined group, the venous angiomata, and then only tumours of the epidermis and of pigment would remain; and this would greatly simplify the definition. But though this anatomical description of the "fiery" moles might possibly hold in Germany, this simplification would arouse no response abroad, especially in England, where the term nævus is practically restricted to the vascular moles; and even this limitation of the moles might be regarded as not sufficiently strict.

The sub-division of our narrower group of nævi is simple enough, anatomically. Here also we have mainly to distinguish proliferative and stagnatory tumours. In the first we would have the soft, hard,

and mixed nævi (without reference to the ultimate pigmentation), also the hair nævi, and most pigmented giant nævi. In the second, the angiomatous nævi, pigmented nævi, and the seborrhœic nævi (seborrhœic warts). The linear nævi, whose position is problematical, might provisionally remain with the proliferative tumours.

By *soft nævi* I understand pretty nearly all those described as soft warts, only with the difference, that the soft nævi permit of a strict histological definition. They are the embryonic deposition of epithelia in the upper part of the cutis, which, by the loss of their epithelial fibrillation, have lost their stiffness. Therefore the tumour which developes is soft, like a plasmomatic cellular infiltration. Hard nævi, on the contrary, are tumours of epithelia which are not deposited in the cutis, and have retained their hard structure.

(α). *Soft Nævi.*

I have just noted, that the investigation of very many cases of soft nævi, as well as the observation of them in the living, has taught me, that the popular view of the constancy of each nævus must be modified. I believe that we are already in a position to indicate the individual stages of development through which the majority of soft nævi pass during life. It will thus be seen, that the multiformity which the individual tumours in any one case often show, where they are present in great number, may be explained as different stages of development of one uniform kind of tumour, and not as so many different varieties of tumour. But equally distinct is a marked contrast between these soft tumours, and externally similar, but hard new formations, which resemble rather the infectious hard warts, or certain flat Keratomata. I have not, at least as yet, found the two forms of nævus—soft and hard—in different parts of the same individual, even where great numbers of one form were present.

Following the external appearance, I divide soft nævi into the four stages of the *sessile*, the *button-shaped*, the *raspberry-like*, and the *molluscoid* (mollusca). The first are found chiefly in infants and children. Where they are not pigmented, one can better recognise them through the diascope than with the naked eye. I commence with the form most frequent in middle age, the button-shaped.

The *soft button-shaped* nævi are microscopically distinguished, as Demiéville pointed out, by columns or alveoli of cell cords and collections, which fill up the whole growth to close on the epidermis, and usually end abruptly beneath it. If we compare the smaller processes of these cords at the periphery, with the larger and thicker ones at the centre, it will be seen, in the button-shaped nævi of adults,

that this new formation occupies the papillary body and the upper part of the cutis. Only exceptionally do we see single cords accompanying the hair follicles or the ducts, down towards the glands. Usually, most of the cutis and the whole of the hypoderm are free from cellular enclosures.

The cell cords consist of small, cubical or elongated cells, rich in protoplasm, which have a relatively large, oval, clear, vesicular nucleus. They are therefore, except for the want of prickles, very like surface epithelia. Further, we see that inside the elementary cellular cords, there is no collagenous or elastic tissue, and no distinct intercellular substance, just as in the epithelium. Mitosis I have not been able to recognise in a very large number (67) of these nævi; in adults, cellular division must consequently take place very slowly. There is an exception to this rule in the development of nævo-carcinomata (which see), where there are found, at the periphery of the tumour, numerous mitoses, inside otherwise unaltered cellular cords.

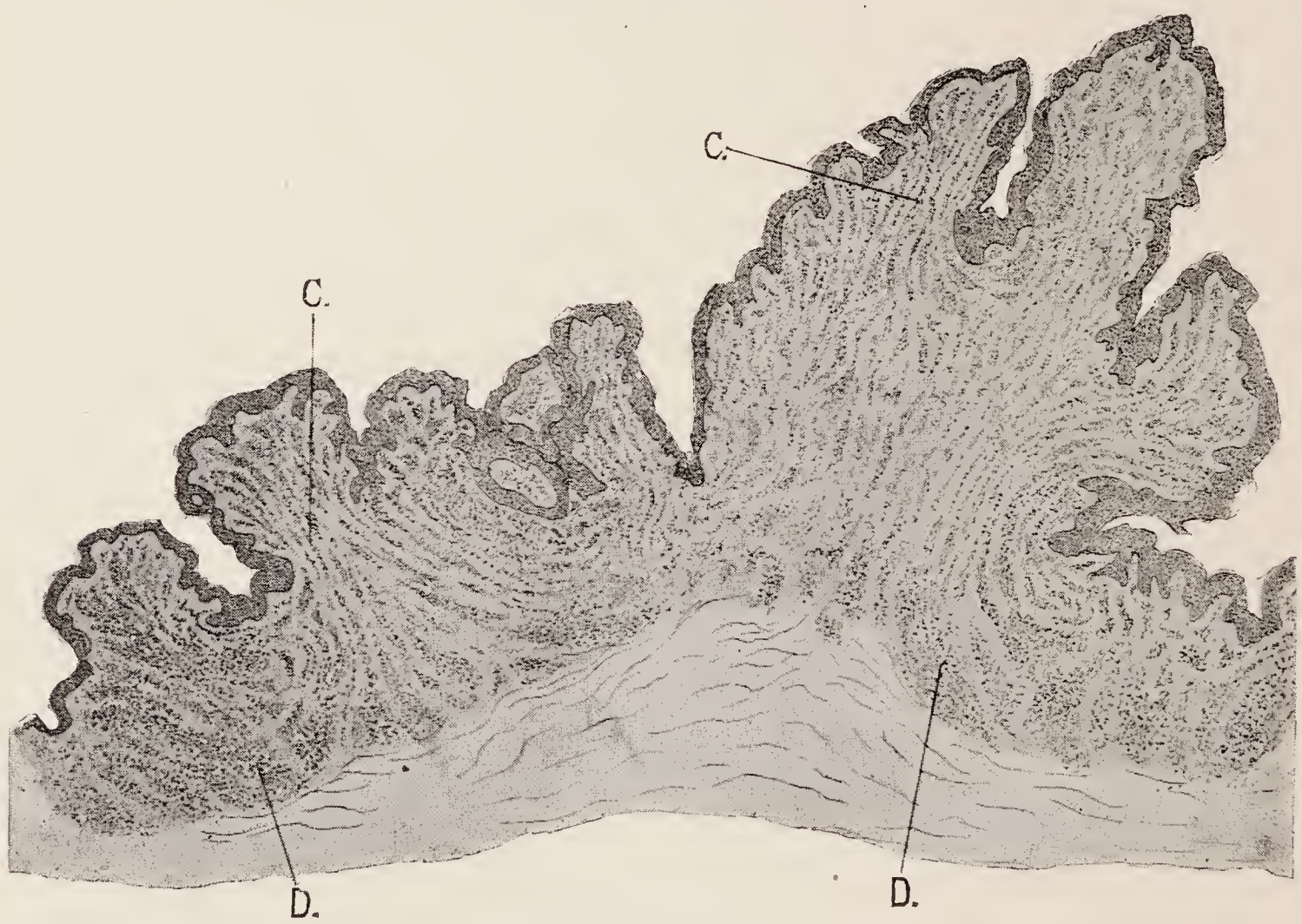

FIG. 39.—Soft Nævus.

Showing columnar arrangement of the cells, which is most marked at the very edge of the mole.
C. Columns. *D.* Denser areas, where the columns are more compressed.

Towards the periphery of the nævus, the cellular cords are better margined, and more purely columnar than inside the tumour and at the base, where they often run together to form coarse, diffuse masses. But the columnar form is no proof that the cells lie inside the lymphatic vessels, that the cellular cords are proliferated endothelium:

in a word, that the nævi are *lymphangio-fibromata*, as v. Recklinghausen has stated. From the authority of this author, his view has been adopted in all text-books. Partly on this ground, partly because that explanation of nævi is found in the classic work on neuro-fibromata, which I regard as one of the best works in the whole subject of cutaneous pathology, I must go specially into this point. The motive for my different view, so far as it depends on purely morphological grounds, will be best evident when we discuss the more important particulars in the structure of the cell cords. Against the view that these are cords of lymphatic endothelium, are the following facts :—

1. The cells never show the regular concentric arrangement, which ought at least to be evident on cross sections of cords.

2. The cell cords never show any regular, well-margined lumen, not even the smallest of them.

3. At the periphery of the button-shaped nævi, the cellular cords are vertical, while the lymph vessels have a horizontal course.

4. The cords in large nævi lie in parallel bundles, and the bundles cross each other at all possible angles. Both facts are against the origin from lymph vessels; for instead of forming columns, the adjacent cords ought to communicate in a plexus; and instead of being crossed in bundles, the gross divisions of the nævus ought to show an almost parallel arrangement. Consequently, in the large nævi, the cords run almost in the opposite direction to the lymph vessels of the skin: the former are parallel in small areas, and in larger areas take various directions, while the latter run, when small, in acute angles, and as a whole, are in parallel arrangement.

5. At the base of the tumour, the columnar character is very frequently absent; while, were the growth from the lymph vessels, the columnar distribution would be better marked towards the hypoderm.

6. Did the cellular columns develope in the lymph vessels, they would, at the periphery, be recognisable as such, would spread out radially, and would give to the tumour a blurred appearance, while the very contrary is the case.

7. The cellular cords in different nævi vary very much in thickness; a fact which is as much against the development in preformed canals, as it is in favour of the dependence of the growth on the surrounding collagenous tissue. The columns repeat, in their size, in the parallelism *en detail*, and in the angular crossing *en gros*, exactly and distinctly the arrangement of the collagenous tissue. If its bundles are better developed, we see between them a more regular columnar form; if, on the contrary, the number of cells predominates, then the columnar form is replaced by an irregular alveolar one. At the periphery,

where the amount of collagenous tissue always exceeds that of the cells, the columnar form predominates; at the base, where the cell masses are mostly compressed, and show few minute collagenous septa, the alveolar form is more evident.

8. The lymph vessels are demonstrably free, and in many loosely-formed nævi, run through as dilated spaces. Now and again, I found the cellular cords at the under margin, reaching right down to a large lymph vessel of the cutis, and here the horizontal limitation of the under border of the nævus was formed by a completely free, wide lymph vessel.

9. v. Recklinghausen found the form of the cellular columns to be similar to that of the lymphangiomata of the skin. This is certainly correct, for a comparison with certain papillary lymphangiomata shows that the form in both is brought about by mechanical pressure, to which I shall immediately refer. But in comparison with lymphangiomata of the cutis and sub-cutis, there is no resemblance.

10. The cellular columns of nævi by no means correspond to the appearance produced by injection of the normal lymph vessels of the skin.

These morphological proofs obtain a satisfactory supplement in the history of the development of soft nævi, which shows positively, that they are not Endotheliomata but *Epitheliomata.** All pigmented and non-pigmented, flat, just elevated nævi which are removed from infants and children, show a direct connection of the surface epithelium, and, in parts rich in follicles, of the prickle layer of the hair follicles, or even of the ducts of the coil glands, with the cellular cords of the nævus. There always accompanies this continual transition of one formation into the other, a metaplasia of the prickle cells into soft, plastic, amœboid clumps, without prickles and without epithelial fibrillation, but which always retain, as a sign of their epithelial nature and origin, their oval, clear vesicular nucleus, and the further property of remaining in connection with neighbouring epithelia, without the intervention of inter-cellular substance. And these metaplastic epithelial collections always show a tendency to snare themselves off from the fibrillated epithelium, as rounded balls and cords; whereupon they are surrounded by the connective tissue of the cutis, and completely isolated.

One finds in these young nævi, very different appearances, according as the epithelial growth into the connective tissue is old or recent, according as it is still going on, or has almost completely ceased. The

* I use the word *Epithelioma* here in the meaning referred to in the chapter "epidermic growths": growths of epidermic cells *without epithelial fibrillation*, while the word *Acanthoma* indicates those *with epithelial fibrillation.*

complete arrest of the new formation of epithelial cords and alveoli, I have never found in the nævi of children. I always found the process of ingrowing and snaring off going on at some part. Once attention is directed to it, one finds in many snared-off, lobulated, pedunculated nævi of adults, the cord formation still going on. (I found it in about half the cases I examined). It therefore never ceases completely, unless the nævus undergoes some degeneration (Molluscoid). That in the carcinomatous degeneration of nævi, a new epithelial growth may come from the surface, and complicate matters, we have already seen in carcinoma.

If the ingrowth and deposit of epithelial nests (Cohnheim's tumour germs) take place in embryonic life, in infants the whole cutis becomes filled with them. They are stretched parallel to the surface, by the parallel new formation of collagenous bundles, are vertically flattened, and only adhere to the surface by oblique and reticular connecting branches. If, on the other hand, the epithelial growth begins towards the end of embryonic life, or in childhood, the cutis proper, which is now firmer, is free from epithelial nests, and only the looser papillary body is filled and distended; in these much more frequent cases, the epithelial nests mostly retain their original vertical position. These two different forms can very well be distinguished in the nævi of adults. The former show underneath, a button-like, swollen nævus of the surface, and a zone with numerous nuclei inside the cutis, in which the individual cells can hardly be separated by the best staining, and which consist of compressed, horizontal, anastomosing, flat epithelial nests, filling the lymph spaces between the horizontal collagenous bundles. The connecting protoplasm is reduced to a minimum, the nuclei are small, but well preserved and closely compressed, and in this atrophic condition they remain during life. These are the rare cases of soft nævi in which the new formation reaches to the under margin of the cutis or even to the hypoderm, and which I have not considered in the morphological description of the button-shaped nævi. The deep lying, very early developed epithelial collections behave as a passive, inert appendage; they remain local, but they do not undergo further growth, nor do they go through the remarkable stages of progressive and degenerative changes, which affect superficial, later developed epithelial nests, and whose presence we can assume from the clinical behaviour of the nævi.

To the changes which distinguish the ordinary nævi belongs especially the *gradual projection over the surface of the skin.* This appearance, to which we owe the somewhat incorrect view that nævi mainly develope only in adults, is at once explained in examining several nævi of different size, from the same corpse, in regard to their

elastin contents. We find that wherever the epithelial nests are luxuriant, all the elastic tissue between them perishes. But since, close to the margin of the epithelial insertion, the elastin remains unaffected, every active and passive movement of the skin must loosen the now

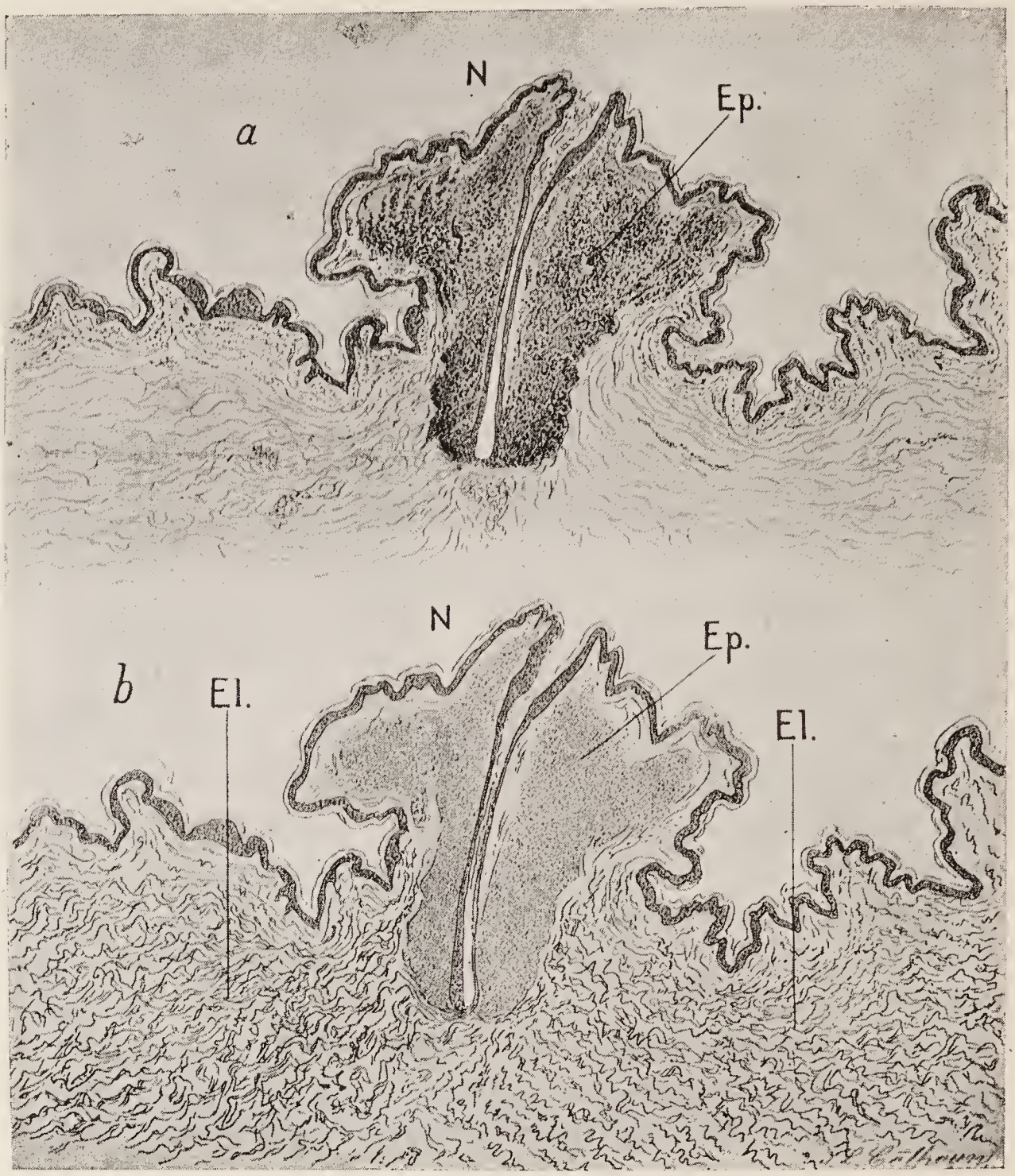

FIG. 40.—"Birth" of a Nævus.

A. Stained with hæmatoxylin to show nuclei. *B*. With acid orcein to show elastic fibres.
N. Nævus. *Ep*. Epithelium. *El*. Elastic tissue.

inelastic nodule more and more from the elastically stretched neighbourhood, and since it is only surrounded by elastin from beneath, it gradually advances upwards. The "birth" of the nævi is thus due to two changes, viz., increase in epithelium, and diminution of elastin inside the cutis. In rising they may take with them enclosed organs, still retaining elastin, such as whole hair follicles.

A second change of the surface, which very much alters the appearance, is the behaviour of the surface epithelium of the soft

nævi. If we for a moment ignore the bygone epithelial ensnaring from the surface epithelium, the latter is much stretched by the insertion of epithelial nests in the upper part of the cutis; the prickle layer is reduced to a thin layer, and the ridge system is partly flattened out. Some ridges, however, though changed, remain and form septa in the uppermost zone of the growing nævus, which usually contains several papillary loops and epithelial cords, and is no longer comparable to the papillary body of the neighbourhood. In these cases, the external surface of the button-shaped nævus is still smooth.

The less the constant epithelial growth of the surface in such nævi tends to the formation of new, completely snared off epithelial nests, the more tendency does it show to the production of ordinary epithelial ridges, of the type of prickle cells. This is evidenced in two different directions. If the growth appear on many new areas of a surface without ridges, there is formed a narrow, superficial, new ridge system, and since the epithelium of these new ridges cornifies, and the horny masses separate, the button-shaped nævus acquires a fine lobulated, glandular appearance. But if, as often occurs, only persisting, older epithelial ridges grow, the tumour is cleft in a coarser manner, and after the cornification of these deep, thick epithelial ridges, and the falling out of their horny layers, there remains a coarse, deeply-lobulated, raspberry-like nævus. The further the epithelial ridges are from one another, the larger are the constituent parts; the broader they are, and the deeper cornification extends, the more loose and movable are these elements. From the basis of these epithelial ridges, there is a tendency in the larger tumours to the production of secondary epithelial ridges, which may lead to two noteworthy occurrences, viz., first, to the snaring off of an isolated part inside a nævus, which then projects more rapidly than the rest of the growth (Nævus in nævo); and second, to the complete interposition of certain elements, which then hang by such thin pedicles, that they are readily torn off (sequestration of parts of the nævus). Where we have this "*raspberry transformation*," the nævi always remain doughy and compressible; a slight degree of acanthosis of the surface does not suffice to give them the hardness of "hard nævi."

Recollecting, then, this genesis of soft nævi, and their further development in adults, we can understand all the different forms of distribution of the cellular cords. This is—and here I ignore the nests included in the embryonic connective tissue—always dependent on three factors: 1, the amount of the snared-off epithelium; 2, the strength of the elastic force; and 3, the intensity and extension of the secondary fissuring by the persisting surface epithelium. Since the act of snaring is done by the cutis, most nævi show (even if the

surface is semi-spherical), on their base, a closer compression of the epithelial nests, up to complete coalition, and thus they appear on section, fan-shaped. The upper parts at the epithelial margin, show, on the contrary, the epithelial cords isolated; and the connective tissue between them, when the constriction is considerable, has a tendency to become œdematous. In its fullest development, this forms the molluscoid nævus (see below).

There is little of importance regarding the other constituents of these nævi. The collagenous tissue disappears under the pressure of the cords, by no means to the same degree as the elastic fibres, but the disappearance is more regular and more widespread, especially at the base of the nævus. In other places it shows a slight swelling. There is sometimes an appearance of new formation, caused by a degeneration of the epithelial nests, which become unstainable, and resemble the surrounding tissue (see below). The number of mast cells is, at the first glance, very varied. They are often scanty, or are altogether absent in patches; in other cases they are regularly distributed over the connective tissue of the new growth, and in some places at the base and in the surroundings are present in quantity. But in general, they are found in their normal position at the margin of the epithelium. I have not found them inside the epithelial nests. In view of the amount of sunken epithelium on these places, the sometimes remarkable number of mast cells is not striking.

Much more important is the presence in the soft nævi of *pigment.* Exactly as in certain carcinomata (Xeroderma pigmentosum, cancer of sailor's skin, Nævo-carcinoma), the metaplasia of the prickle layer is in direct connection with the pigmentation of the affected epithelia. In slight pigmentations (Nævi spili, Lentigines), the growth of the prickle layer, and its round and cord-shaped ensnarings from the rest of the epithelium, are limited to those areas which have taken up pigment. The melanotic pigment here is often so dense in and around the cells, that the appearance is that of simple collections of pigment, here and there enclosing well preserved nuclei. Indeed if, in order to find out the youngest stages of soft nævi, the observer takes those of infants and children, and in order to be more certain, restricts himself to the more easily-found pigmented nævi, he will certainly get the impression that pigmentation is a necessary to the epithelial growth and metaplasia. For here, the processes always coincide. But if he will investigate unpigmented nævi of infants and children, and follow their behaviour in adults, he will find that, without pigmentation, the epithelial growth and snaring-off of individual nests may take place in exactly the same way. Only, it certainly appears to me, that the loss of the prickles is much more rapid and earlier, where pigment is present, so that some

softening effect on the epithelium, and especially on the epithelial fibrillation, can hardly be denied. While the unpigmented epithelial buds may penetrate pretty deeply into the cutis before the ensnaring commences, we find at the pigmented spots a separation commencing inside the unproliferated prickle layer. And while the ensnared, unpigmented epithelial nests often show angular and toothed forms, and may contain remnants of prickled epithelia, the pigmented epithelial nests, from the commencement, have the form of perfectly round balls, in which every trace of epithelial fibrillation is lost. The snaring-off of such epithelial collections may very well be compared to the dropping of a viscous fluid. On all the flat pigmented moles of children which I have examined, this "dropping" of the epithelium into the cutis could be observed accompanying the pigmentation.

The changes of the *button-shaped swelling* and the *raspberry-like cleavage*, previously considered, are the ordinary changes of soft nævi in adults, which take place slowly, from puberty up to old age. The nævi may be arrested at any stage of this development, or they may undergo further changes, which are described as *fibromatous* and *molluscoid* degeneration. Beyond these changes they do not go. They are usually met in this stage only in old people, but with more rapid development may also appear in middle age. The *molluscoid nævi* are more frequent than the fibromatous, and are familiar as Molluscum and Fibroma molluscum. They are often confused with the soft neuro-fibromata, or regarded as a special form of tumour; but their connection with button-shaped and raspberry-shaped nævi has been noted by only few authors, and is certainly not sufficiently estimated. As a fact, most isolated mollusca are nothing but much altered, soft nævi.

> By molluscum I understand simply berry-like, pedunculated, small, flabby, pale tumours, which are sometimes isolated, sometimes multiple, but always irregularly distributed, and usually occur along with other less degenerated nævi. They are soft, compressible, and often wrinkled like raisins. Since the neuro-fibromatous nature of most of the systematised soft fibromata of the skin has been recognised, it is a mistake to apply to them the less definite name of Molluscum or Fibroma molluscum. I prefer to limit that name simply to the pedunculated forms here described, which are evidently developed from button-shaped nævi.

That the defined mollusca really develope from soft nævi, is best seen in those berry-shaped nævi in which the fissuring is advanced, and at the same time more marked constriction has commenced at the base. Then one always finds certain protuberances, which reach over the others, and whose sharp angles have become rounded, and their consistence softer. Sometimes parts of such a nævus, snared off by a thin peduncle, reach high over the rest, and represent small, soft,

œdematous or wrinkled *mollusca in nævo.* If one investigates those molluscoid processes of a large berry-shaped nævus, it will be found that the periphery of the cellular cords has partly degenerated, partly disappeared, but is still well preserved in the centre; and one can consequently study here the *molluscoid degeneration of nævi.* The fully developed, isolated mollusca often show no traces of the epithelial inclosure, and are consequently little suited for the study of their development. I have found among thirteen isolated mollusca, three, in which, in different parts, epithelial cords were recognisable, while in the others, degenerated remnants were visible.

There can be no doubt that it is the constriction of the base which causes the molluscoid change. The youngest mollusca are nothing more than œdematous, button-shaped nævi, with dilated lymph spaces, and softened, sodden connective tissue. But very soon the influence of stagnatory œdema is evident on the enclosed epithelial nests. With an ordinary nuclear or protoplasm stain, there are evident quite unstained parts at the periphery, which, with a low power, appear like patches of œdematous connective tissue. But with a higher power and a small diaphragm, it is plain that they are very much swollen epithelial nests. Every individual cell is transformed into a large round bleb, whose nucleus is compressed and atrophic, or is broken down into several granules. Where the epithelial nests have completely perished from colliquation, there are gaping lymph spaces. In this way the nævus gradually loses, from the periphery to the centre, its epithelial contents, and consequently becomes ever more flabby and wrinkled. The final stage is represented by a tumour, which contains, in its interior, a loose, rarefied, elastin-free connective tissue, clothed by a very thin epidermis, and containing no penetrating epithelial ridges, follicles or coils. At the constricted base there usually enters a pretty large, vascular cord, with an artery and one or more wide veins, which inside the tumour are surrounded by very wide lymph spaces.

Much rarer than the molluscoid change is the *fibromatous.* This usually appears on simple button-shaped nævi, the looser connective tissue septa of the epithelial nests thickening and separating the latter further and further from one another, and from the surface of the nævus. The new formation of epithelial nests is completely arrested, so that these elevated, constricted or button-shaped tumours clinically resemble unusually firm nævi, and are recognised histologically only by the diminished remnants of epithelial cords. The fibromatous nævi may also become pedunculated like the mollusca, but they never form such flabby, compressible growths.

It is questionable whether a *lipomatous* degeneration of soft nævi is a frequent occurrence. One certainly meets not infrequently,

especially on the neck and genitals, pedunculated, pear-shaped growths of the size of an almond to a walnut, which are not soft and compressible, but of pretty firm consistence, and on section consist almost exclusively of fat. It is quite certain, that these pedunculated lipomata do not owe their origin to snaring off of the normal panniculus. At most, some abnormally-formed fat lobule in the cutis, very much swollen, might, in this way, be projected over the surface of the cutis, but never a part of the subcutaneous tissue. But we see on the nævi themselves, that the epithelial nests enclosed in the cutis never ascend with the others over the surface of the skin, for they are surrounded on all sides by elastin. If one examines further a series of these tumours, a gradual development of fatty tissue inside them cannot be denied. The smaller ones contain it distributed along the vessels, and gradually increasing fat cells may fill the whole space from the vessels to close on the epidermis. But how the fatty tissue is developed in these cases, is to me a mystery. To those who believe in a spontaneous development of adipose tissue in any part of the connective tissue, the cause of its appearance is not worth investigating. But for my theory of the connection of the fat of the skin with the oily glands of the skin and especially with the coil glands, there is, I candidly admit, a great difficulty. In spite of numerous careful investigations, I have only twice been able to find a coil gland embedded in the lowest part of the tumour; and in one osmium preparation it was full of fat, so that here the explanation of the new formed fatty tissue in the molluscum was explained. But in the others, in which adipose tissue was abundant, and the epidermis now and again injected with fat, I found neither coil nor sebaceous glands. I have kept in view, that possibly the epithelial cords in their distribution might undergo a fatty degeneration, but I have not discovered it; they always undergo simple colliquation. Either, then, there must exist some unknown source of fat, or I have over-looked the fat-supplying glands. In the former case, these growths possibly form a peculiar section of tumours, or a special class of the nævi. For the present, I have placed them with the molluscoid nævi, for in two cases at least, I believe that I was able to determine the secondary deposit of fat in a molluscoid nævus.

In addition to the two changes described, which must be regarded as the regular changes of age, I have now and again found partial degenerations, which, however, are too occasional to be regarded as the ordinary appearances of these growths. These were marked swellings of certain epithelia and collections of epithelia, both in the epithelial nests and inside the proliferating surface epithelium. These lose part of their staining power, and form cloudy, finely granular, not homogeneous masses, in which nuclei are usually clearly recognised. The

epithelia, thus altered, run together, and exert some pressure on the neighbouring connective tissue, so that they evidently have a pretty firm consistence. They show no tendency to colliquation and vacuolisation. Sometimes they also contain pigment.

(β). *Hard and mixed Nævi.*

The much better comprehension which we have obtained of the soft nævi, namely—that they depend on germs of epithelium snared off in the embryonic period, or later, contrasts all the more strongly with our ignorance of the other nævi.* There appear in many cases, circumscribed, warty protuberances, which, on account of their stealthy development, their appearance in childhood, and their hereditary site, are regarded by the laity and profession as moles, but which, on microscopical examination, appear as purely epidermic thickenings, without any trace of epithelial germs enclosed in the cutis. Here, then, Cohnheim's theory, so suitable to the soft nævi, is useless. We cannot conceive of superfluous epithelial germs, which are enclosed in the epithelium itself and do not go through the process of normal cornification, and which in later life can cause tumour-like formations, locally. We can neither explain such an occurrence, if these supposititious germs had the structure of the ordinary epithelium, and were thus in direct connection with the epithelial fibrillation; nor can we understand how a ball of embryonic, or non-fibrillated, or any other kind of epithelium, could resist the constant throwing off of the rest of the prickle layer. There is no other possibility of explaining that congenital anomaly of epithelium which leads, in different periods of life, to the development of nævus-like tumours, than that the epithelia of a definite region of skin have some innate property, which can be communicated to their descendants, and which the latter at some time or other evince in the development of a tumour.

If these "hard nævi" always consisted mainly of horny substance, the matter would be easier. One would then have to assume only a remarkable coherence of the epithelia, which must gradually lead to "callous" thickenings, and this would explain the cause of their long unchanged persistence. But half of the hard nævi consist mainly only of thickened prickle layer, whose unchanged condition is by no means so easy to explain.

Clinically, these nævi are flat, hard moles, of the size of a lentil to that of the palm of the hand, whose colour varies from that of the skin, to the greyish-yellow and dark brown of dark horny substance. Especially the larger ones, which are broken up by the movements of the skin into stalactiform prisms,

* Here I exclude the angiomatous nævi.

tend to show out dark from the surroundings, although all these moles, in contrast to the soft ones, only rarely contain true pigment. The smallest ones frequently appear in groups, especially on the trunk; they have a rough, finely granular, papillary, often furry surface, and are, on account of their light colour and roughness, often better felt than seen. Now and again they show grooves, but never hairs.

Histologically, one has to distinguish in the hard nævi, two main groups: the *acanthoid* and *keratoid,* according as the thickening is mainly in the prickle or horny layer. The latter are by no means to be regarded as a further development of the former, for the acanthoid hard nævi are also distinguished by anomalies of cornification (horny pearls), which, however, do not lead to heaping up of the horny substance on the surface. In order to give an idea of the frequency of these less familiar nævi, I give a table of their relation to the soft nævi, as shown in eighty-four isolated, small nævi,* taken at random from the corpse.

Soft Nævi.		Hard Nævi.	
Sessile nævi from children . .	16	Acanthoid	8
Button and berry shaped from adults	36	Keratoid	9
Mollusca	15		17
	67		

Thus there are about four soft nævi to one hard. Transition forms between the two do not occur; occasionally they are combined. Of 87 tumours, I have only thrice found a hard nævus on the surface and a soft one underneath. These three mixed nævi afford, rare as they are, a valuable proof of the nævus nature of hard nævi; so much at least we understand of the similarity between the two forms of nævi.

In contrast to the button-shaped soft nævi, the acanthoid hard ones only rise gently over the level of the skin, and pass, even microscopically, without any sharp margin, into the surroundings. Very gradually the prickle layer thickens to four or eight times its original size, and shows at these places a coarser furrowing. The cutis underneath the acanthoma is almost completely normal, shows no trace of epithelial nests, and at most only a slight thickening and modification of the cells around the vessels. The papillary body is quite flattened down, and the nævus usually possesses only very fine, straight papillæ. While the soft nævi are distinguished by the very multiform ridge net, in most hard nævi, and in all the older ones, the epithelial cutis margin is almost horizontal. There are therefore no epithelial depressions which reach lower than the ridges of the healthy skin around; and thus this form of acanthosis is limited to a lateral compression and thinning of

* This does not include the larger, the linear, the hairy and mixed nævi.

the papillæ, a thickening of the supra-papillary prickle layer, and a thickening of the ridges which are present, whereby the ridge system is ultimately flattened into an almost homogeneous epithelial plate, with a flat margin towards the cutis, and only scantily penetrated by fine papillæ.

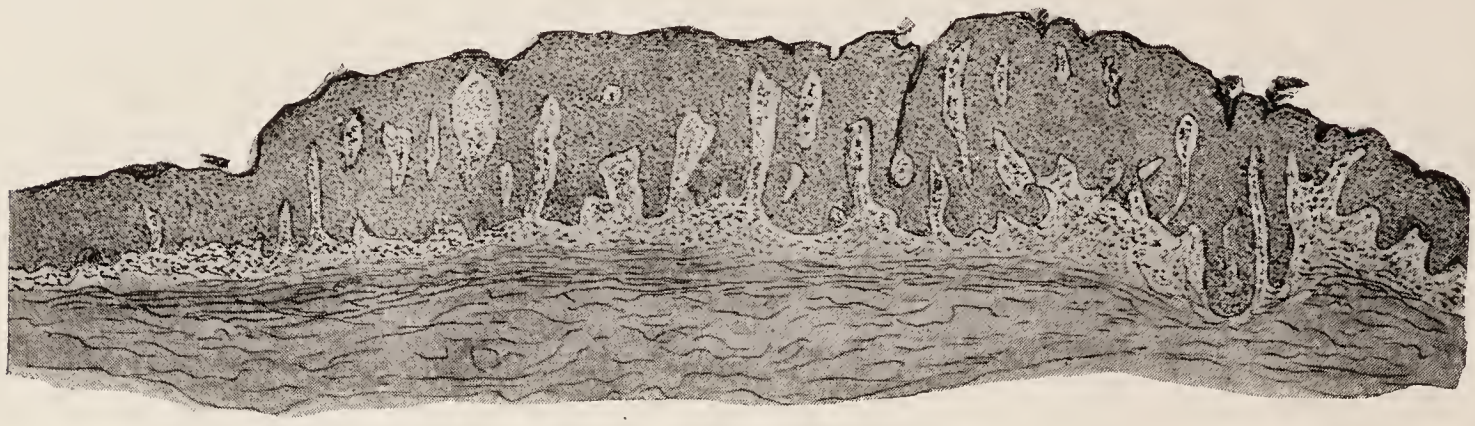

FIG. 41.—Acanthoid hard Nævus.

Showing thickening of the prickle layer, and no snaring-off of epithelium.

A result of this form of epithelial thickening is a remarkable appearance, which may almost be said to be pathognomonic of these hard nævi. One finds in them almost always horny pearls, which, separated by a single layer of prickle cells, rest almost directly on the cutis margin, while above them, well-formed cylindrical prickle cells, surrounding the heads of the papillæ, appear. In many places where these horny spheres almost approach one another, the reverse condition is seen: the horny layer on the cutis margin, and over it the prickle layer, penetrated by papillæ. The appearance is explained by the previous transformation of the prickle layer into a homogeneous plate, inside which only thread-like papillæ ascend, to end with club-like swellings; and further, by the lesser tendency of these nævi to cornification. This only appears in the intervals between the papillæ, and advances deeper and deeper, until it almost reaches the cutis margin. Since these horny collections are enclosed and cannot fall out, they form gradually, along the cutis, a series of horny spheres.

The *keratoid hard nævi* may be divided into two groups, according as acanthosis precedes them or not. In the latter case, there develope simple, wavy, lamellated, dark yellow, horny plates—a rare type. In this case the prickle layer is the thinner, the older the nævus is, the papillary body is flattened out, the cutis margin runs absolutely smooth, and the horny layer shows a horny consistence, and a tendency to break up into prisms, from the movements of the skin.

Where there was a precedent, noticeable thickening of the prickle layer, there developes a more warty structure, for the papillæ which were preserved during the acanthosis, persist in the keratoid stage. The older these nævi, the more abruptly wavy is the lamellation of the

horny substance. The falling-out of the horny collections leads to a bursting of the surface, and prevents the tearing of the horny structure. Many of these old nævi are so completely cornified, that it is most difficult to find the very scanty papillæ, and the single row of prickle cells, which still unite the thick horny masses to the cutis, while they appear to be only loosely seated on it. But however marked the cornification, the horny nævus never resembles a cutaneous horn; there is never any so-called medullary substance. The horny substance is firm enough, but the formation of papillæ and their supply of blood are too scanty.

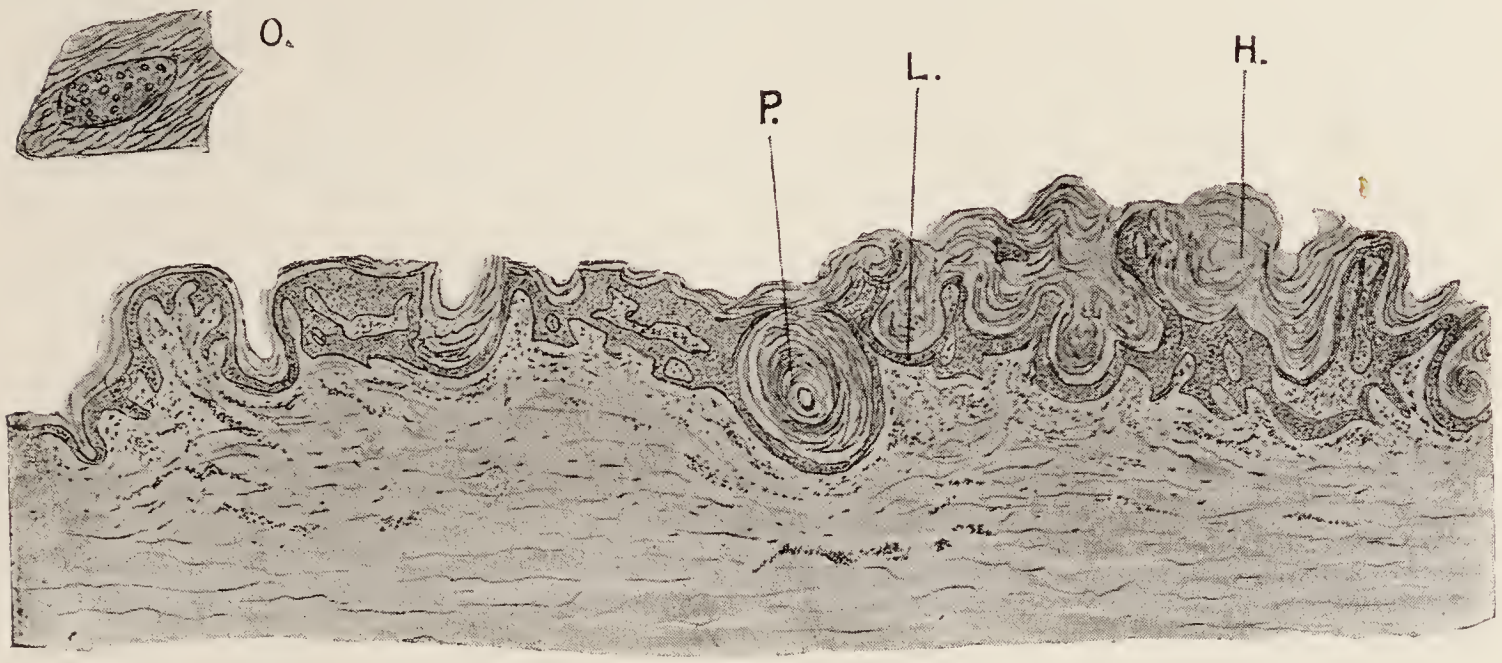

FIG. 42.—Keratoid hard Nævus.

Shows thickening of the horny layer; the prickle layer *L.* much reduced in thickness. (Horny layer *H.*)
P. An enclosed follicle containing a horny sphere.
O. The original size of the growth.

In some of these cases (thrice out of nine keratoid nævi) I found groups of follicles enclosed in the nævi, in which the hair follicles were otherwise always atrophic. Twice there was complete cornification of the follicle, which showed on section large horny spheres, growing as appendages of the horny layer, and reaching almost to the cutis. In one case, instead of this, there was a hypertrophy of the sebaceous glands underneath the horny nævus. These follicular complications seem to be restricted to the hard nævi. I have met them in mixed nævi, but never in the pure soft ones.

To these hard nævi is probably allied the case of Nævus porokeratodes, recently described by Hallopeau and Claisse, of which, however, there was no histological examination. But the seat on the sole of the foot, and the transition found by the authors, of simple dilatations of the sweat pores into the horny bordered craters, indicate sufficiently the localisation of the nævus in the sweat pores.

Finally, I should note that the hard nævi may combine with other

congenital growths instead of with soft nævi. Thus I have a hard nævus, which, in addition to a hypertrophy of the sebaceous glands on the surface, showed a combination in the depths of the skin with a leiomyoma and a spiradenoma.

(γ). *Hair Nævi.*

The hair nævi are rarely simple, circumscribed hypertrophies of the hair.* Usually, they are simply very hairy, soft, pigmented nævi. The simply pigmented but otherwise smooth hair nævi are also to be reckoned with the soft nævi, and they correspond to the young sessile instances of the soft nævi, not yet elevated over the level of the skin.

The main histological interest in connection with hair nævi, centres in the question: what is the relation of the hair follicles to the epithelial new growth? After examining four more or less pigmented hairy nævi, which showed all stages, from the absolutely flat to the semi-spherical soft, I think that I can shortly answer this by stating that the ensnaring of the soft epithelia from the surface takes place in the ordinary way, and that the flat nævi show more epithelial nests in the cutis, the button-shaped in the papillary body—exactly as in the non-hairy ones. The only difference is, that here numerous epithelial nests are collected around the hair follicles, though usually only up to the middle region of the hair follicles. From comparison with certain nævi of infants, whose follicles are not yet atrophied, I conclude that this is due to the fact, that the prickle layer of the hair follicle, even at an early stage, has provided, by snaring off, a great part of these epithelial nests. In virtue of the thinness of the follicle in the middle hair region, this is most likely to occur there, somewhat less so in the upper third, and not at all in the lower. To this is evidently due the fact, that the under third of the hair shows its surroundings quite free from epithelial nests, while the middle is closely surrounded by them.

In one of my four hair nævi, the process was still going on. The longitudinal sections of the follicle, from whose middle and upper regions (from the former more than from the latter) a dense epithelial growth ran in all directions in horizontal cords between the collagenous bundles, have a remarkable appearance. It is hardly conceivable how the particularly strong hairs found in the follicle, could complete their growth undisturbed, while in the hair follicle a central part proper does not exist; for here the prickle layer of the follicle passes directly into

* Such apparent cases should be carefully examined to see that there are not, in the neighbourhood of the hair follicles, ensnared epithelial nests.

the new growth of the cutis. Now such a defect does not necessarily disturb the papillary growth of the hair; but the ascent of the hair into the follicle, which requires an active epithelial proliferation of the upper region, may very well suffer in such hairs, and perhaps not take place at all. Possibly the persisting hairs in some nævi are due to this aberration of the hair, by the direction of the epithelia of the central hair region being outwards instead of inwards. Most soft nævi have little hair, because, with the marked epithelial growth into the cutis, the hair growth, like the surface epithelium, cannot assume great dimensions. An actual atrophy of the hair follicles could be induced by the most different influences,* only if they met the hair follicle shortened, and the hair as a bed hair. These conditions are fulfilled in the change of the hair of infants; and if at this time an abundant production of epithelium, or a greater pressure on the shortened hair follicles takes places, they readily lead to complete loss of hair in the nævi. But if the hairs of the nævi pass this, and similar critical periods, which we know are repeated after each falling-out of the papillary hair, there is not only no cause for falling-out, but, by the disappearance of the follicle membrane, and the extension of the epithelia outwards, it may actually be hindered. With an active blood supply, the hairs thus detained may become specially strong.

Whether this explanation of the existence of thicker hairs on certain soft nævi applies to all cases, future investigation must show. Possibly there are other factors. For in my cases also, only a few hairs are in connection with epithelial nests, and for the others we must assume that previously such a connection has existed. It is in favour of my explanation, that the hard nævi, which show no epithelial ensnaring, are hairless.

Except for the greater length and thickness of the hairs, I have found on the hairy nævi no other deviations from the normal. Pigmentation is limited as usual to the surface epithelia and the upper third of the prickle layer of the hair follicle—to the parts exposed to light.

(ϵ). *Giant Nævi.*

Giant nævi occur in the most varied form, size and extension. Some of them approach the elephantiasic forms, certain parts of the nævus, especially on the legs, hanging down like sacks, and constantly increasing under the influence of gravity; others pass imperceptibly into the smaller pigmented and hairy moles, with which they are almost always combined at the commencement. In most cases, as they extend, so does the amount of pigment and hair: these nævi are often compared with animal's hide.

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* I exclude here the pressure of subcutaneous growths, which directly affect the papillary hairs, but this also induces at first only a shortening of the follicles, and then complete atrophy.

v. Planner has given a very thorough and exact description of such a hide-like, dark pigmented nævus, which is the first instance of the description of the peculiar relations of the pigment to the degeneration of the epithelia, and the formation of pigmented fragments and pigmented balls from the prickle cells. But the author did not note the disappearance of the fibrillæ of the epithelium, and the epithelial nature of the large cells in the connective tissue. He excludes the origin of the pigment from the blood vessels, in his case.

Joseph and Ranke found, in similar cases of giant nævus, exactly the same conditions of enclosed cellular cords as in the ordinary soft nævi.

I have examined three very extensive, elevated, pigmented and hairy moles, which were almost giant nævi, and found everywhere just the same conditions as I have described in the soft and pigmented small nævi. The more marked swelling over the surface, was proportional to the enclosure of epithelial nests, and the folding of the surface to the penetration of the nævus by long epithelial ridges from the surface epithelium, and their secondary cornification. Here also, certain hair follicles participated in the supply of epithelium to the connective tissue, and so did many sebaceous glands, so that now and again isolated sebaceous cells are found embedded in such epithelial nests.

(ζ). *Nævi Lineares.*

I have used the name Nævus linearis, provisionally, as a non-committing expression for all those nævus-like structures which are arranged in lines and streaks, and which maintain definite directions on the skin, so that all new formations of this variety, however different they may look externally, resemble one another in their topographical position inside these regions. They have always attracted attention, and were described by v. Baerensprung as Nævi unius lateris, and by Th. Simon directly as Nerve nævi, and brought into some obscure connection with the nervous system. At the time of the discovery of trophic nerves, it was supposed that they had some connection with them, while in general we are now inclined to assume, as their cause, a congenital tissue difference not especially related to the nerves. L. Philippson has shown that some of them coincide with Voigt's lines, *i.e.*, the marginal lines of the nerve areas of the skin. Hallopeau shows again that several of the Paris cases (Baretta) do not correspond with this arrangement; and Heller recently thought he could recognise a connection with the lymph vessels of the skin.

The external appearance, apart from the remarkable and unexplained topography, is that of old neglected cases of hard nævus. Such was the first of the five cases which I have examined—all of which affected the under extremities of children. It had previously been recognised as a "local ichthyosis." Two others of my cases were similar; but the dry horny layers were in places more scaly, and now and again there was a spontaneous reddening and swelling of the base of these streaks, not seen in hard nævi, and which gave

to the individual spots almost the appearance of Psoriasis patches. In two other cases, the character of the streaks was still more inflammatory, and almost resembled a chronic eczema. So far as the history goes, the affection began quite suddenly, with the appearance of reddened streaks. In one case, by prolonged painting with iodine and clove oil, I was able to cause the disappearance of the new growth.

This personal experience of five cases of the affection, which in spite of their differences are alike in their topographical relations, will suffice, better than numerous literary proofs, to show that this nævus-like affection, in its acute commencement, its inflammatory periods, and the change of its external type, has a course in general strange to nævi, and will perhaps necessitate its being placed in another category.

The few anatomical facts, instead of clearness, only bring confusion. Hallopeau published a case of Nævus linearis of the arm, which he characterised as Nævus pilo-follicularis. The eruption consisted of small, light red papules, each having at its apex a horny plug, from which protruded a lanugo hair or a long sebaceous concretion. In the surroundings of some plaques, the hair was excessively developed. Apparently there was no microscopical investigation.

Then we must note the case of Petersen, which I have already mentioned above under the acquired syringadenomata, and which was observed as a "Nævus unius lateris," in a girl of twenty. As there stated, the glandular tumours found, differ markedly from the syringadenomata developed from embryonic germs. Elliot has recently published a similar case to that of Petersen (p. 812), which should also be considered there. These two analogous cases, taken together with the "follicular" nævus linearis of Hallopeau, show that nævi lineares may develope from the accidental arrangement of scattered areas of disease, which correspond to the individual organs of the skin.

Elliot described a case of Nævus unius lateris in a young man, which was localised at the region of the shoulder-blade. It consisted of a dozen pea- to bean-sized nodules, of which the larger, externally irritated, had some time since taken on a red colour and a warty appearance, had become covered with crusts, and readily bled.

Elliot found a cystic dilatation of the coils and ducts, and even of the sweat pores. This was brought about by a proliferation of the epithelia of the whole coil, and their secondary degeneration, which led to the production of wide lumina, of irregular form. While on the coils there was only a concentric enlargement of the diameter, on the ducts, shortly before their passage into the sweat pore, there were tap-like outgrowths, which were indented by papillary excrescences; Elliot therefore describes the whole affection as "intra-canalicular adeno-cystoma." For the determination that this was really an ingrowth of papillæ, and that the appearance was not due to epithelial

growth, the recognition of cell division on the apex of these connective tissue excrescences would have been necessary.

Two of my cases of Nævus linearis showed different appearances. In one, the prickle layer was hypertrophic, without sending processes into the cutis, and without markedly increasing in thickness. It was as a whole thrown into folds, *i.e.*, it was moderately widened, but appeared like a very wavy ribbon, flattening out the papillary body under the deeper folds, and compressing it at the seat of the higher ones. Such an appearance agrees with the hypothesis of a simple epithelial excess. On a horny papule of this case, there were marked acanthosis, and very marked hyperkeratosis. Inflammatory appearances were absent or very slight. Here the diagnosis of a *hard nævus* would have been justified. In the follicles and coils, no appearances of growth were present.

Another case showed, on the contrary, the most evident signs of superficial inflammation. It exhibited not only a leucocytosis (which might have been the result of treatment), but a growth of the connective tissue cells of the papillary body, down to the sub-papillary vascular net. Then there existed everywhere a marked, mainly interpapillary acanthosis, and a parakeratosis, with accumulation of nucleated horny scales, with scattered vesicular formation, widespread inter-spinal œdema, abundant mitoses, and emigration of leucocytes, so that there was a remarkable resemblance to the papule of chronic eczema or Psoriasis (*q.v.*). Had the clinical appearances not been totally different, and had the eczema organism not been absent, one would have had to diagnose, histologically, chronic eczema. There was no question of a resemblance to either soft or hard nævus, and there were no appearances of growth in the glands and follicles.

There consequently exist, in spite of the marked analogy in topographical distribution, both clinically and histologically, the most striking differences. Either we are dealing with topographically similar, but fundamentally different affections, and then the group of linear nævi must be broken up and the true nævi put in the nævus group. Or it is a uniform affection, which may develope through acute stages, into dry, keratoid, nævus-like tumours, or may be localised in the different epidermic structures. Then it still ought to be definitely separated from the rest of the nævi, and given another name. This affection is in any event a good starting-point for a fresh study of the whole question of nævus.

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(f). *Elephantiasis congenita fibrosa.*

Congenital, fibrous Elephantiasis appears either in the form of regular thickenings of the skin of the extremities, genitals, more rarely of the head, or in the form of a distinct, circumscribed, cutaneous fold, which usually projects from the trunk or neck, and hangs down in a lobulated flap. Neither form is anything like so well known as the nævi and neuro-fibromata, and they are much in want of microscopical investigation to define them from these growths on the one hand, and from infectious, acquired Elephantiasis on the other. We are therefore dependent altogether on conjectures, which in the former point to a stagnatory fibromatosis from innate vascular anomaly, and in the latter, to a nævus-like cutaneous excess, affecting the whole skin, and not the epithelium alone.

To the former type belong the very interesting cases in the family described by Nonne, in which, in several generations, Elephantiasis congenita was hereditary. It was mostly present as a formless thickening of the leg and back of the foot. The hypertrophic cutis there was firm, but could be pitted, the depression being long persistent. It was thrown into deep furrows at the joints, and between them was swollen and cushion-like, but otherwise smooth, normal in colour, and carrying hair. The nails, the lymphatics and the bones were in all the cases normal. Only the large saphenous vein showed, in two cases, a cord-like hardness, and could be readily palpated. These changes were always present from birth, and grew, precisely like nævi, along with the development of the whole body, without causing any disturbance. There were never any accompaniments such as Dermatitis, Lymphangitis, Erysipelas, or fever. Nonne ascribed these cases to an intrauterine, hereditary anomaly of certain segments of the lymphatic system; but the palpable change of the large saphenous vein is to my

mind sufficient to explain the increased difficulty of venous outflow, the regional hypernutrition in utero, and thus the stationary, nævus-like elephantiasis (compare the analogous change of the saphena in the case of Southam, under Elephantiasis streptogenes). Similar cases of hereditary elephantiasis were noted by Virchow and v. Recklinghausen.

The other form of Elephantiasis congenita is Pachydermatocele (Mott), the Elephantiasis fibrosa of Esmarch and Kulenkampff, which, however, must be separated from the other forms of "lobulated elephantiasis" of the latter authors (the elephantiasic neurofibromata). They are congenital moles of the upper half of the body, especially of the neck, which, along with the bodily development, very slowly grow, and develope into dark pigmented, soft, elastic, enormously large folds of the skin. These overlap one another and the healthy surroundings, and fall from the neck in the form of ruffles. The tumour in Mott's case weighed, after excision, nine pounds, and consisted only of hypertrophic skin and subcutaneous tissue. A large series of similar cases is collected in the works of Esmarch and Kulenkampff (pp. 202 to 210), of which many were probably elephantiasic neurofibromata, and others (cases of Tilbury Fox, Bruns, Pollok) certainly mixed forms of cutaneous hypertrophy, with neurofibroma developed from below. The firm, fibrous character of the cutaneous folds, the impossibility of even partially replacing the masses, and the absence of plexiform subcutaneous cords, would clinically justify the diagnosis of simple cutaneous excess. The development of the growth in later life, although more characteristic of the neurofibromata, does not exclude a congenital, long latent excess of skin. In this connection, the old case of Graf, mentioned by Esmarch and Kulenkampff (p. 204), is very instructive. In it, a saccular elephantiasis of the neck and eyelids was hereditary in one family through several generations, and always appeared between the fortieth and fiftieth years of life. In future we must be more careful in distinguishing between true cutaneous hypertrophies and new formation of neuro-fibromatous tissue, which, after v. Recklinghausen's investigations, is by no means difficult.

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(g). *Hypertrichosis congenita universalis. Trichostasis.*

The abundant literature on the macroscopic appearances of the so-called hairy men includes none on the microscopic appearances, and therefore the explanation of this striking malformation hangs between two extremes. While, on account of the accompanying defect of the teeth, Hypertrichosis was often regarded as compensatory to the diminished formation of teeth, Ecker, from the fact that the hairs in older hairy men remained particularly soft and fine, and always followed the lines of direction of the embryonic hair, came to the conclusion, that it was a restriction of development, just like the defect in teeth. This view is more rational, because it lacks the mystery which all these vicarious formations and functions have, and it also harmonises with the fact, that similar defects of the teeth accompany congenital Atrichia. It must, however, be confirmed by microscopical investigation.

After an investigation, unfortunately only macroscopical, of the Russian hairy men, I arrived long ago at the same theory of an arrested formation; especially as I recognised the relative baldness of infants to be the result of a general casting of the hair shortly before birth, after which the shortened hair follicles do not at once elongate, as, for example, they do on the scalp. To decide the question whether a true Hypertrichosis, or simply an arrest of development in the stage of universal embryonic hair is present, we must first decide the question, whether, in the hairy men, the casting of the hair at birth takes place or not.* Were the former the case, and had the embryonic hair follicles, instead of becoming shortened all over the body at the period of birth, retained their double length and their hair, then, in spite of the abundance of the hair in the Hypertrichosis of hairy men, we should be dealing with an arrested development. But if, on the trunk and the extremities, the ordinary casting of the hair had taken place towards the end of the embryonic period, and all the follicles had shortened, but again—analogous to the ordinary occurrence in the scalp—expanded to their original (double) length, and thus given origin to a new and very strong fleece on other lanugo parts of the body, then that would be a true Hypertrichosis, analogous to the partial hypertrichosis of puberty, the climacterium and senility.

It is by no means necessary to assume that only one of these two methods of development occurs. Indeed, I think it probable that both varieties exist, for the descriptions of the hairy men differ very much (the Russian hairy men on one side—Pastrana and Krao on the other).

* Since this histological definition of stagnatory formation is evidently not understood in the very valuable critical review of Hypertrichosis by Geyl, I must once more explain it.

In favour of a true universal hypertrichosis are the more marked regional differences; in favour of the persistence of the embryonic covering, is a greater regularity of the whole hair, such as was seen in the Russian hairy men. But the point can only be decided certainly, by observing the conditions, both macroscopically and microscopically, at, and shortly after birth. The microscopical investigation is, of course, much the more important, for there may be unknown deviations from the normal process.

The *importance of the periods of hair change* for every form of alteration of the hair, we have already several times considered, *e.g.*, seborrhœic Alopecia. But in the investigations of Hypertrichosis histologically, it has not been sufficiently attended to, or not understood (Geyl). It is clear that the strength of the hair, *i.e.* that peculiarity which produces the clinical appearance of every hairy covering, cannot very well noticeably change in a papillary hair during its resting condition. I never remember seeing an appearance which could have been explained, on the assumption that a strong papillary hair had been directly developed from a mature, but thin papillary hair, by simple widening of the bulb and increase in volume of the papilla. But during every change of hair, we find abundant proof of the increase or decrease in calibre of the new papillary hairs, which develope underneath high-lying bed hairs in remnants of the old follicle, rejuvenated by fresh epithelial growth; or (after a longer time) in the free, outward-growing young epithelial processes. The simple comparison of the upper old and lower young or rejuvenated parts of the follicle, shows whether the new hair will be of the same calibre as the old, or thinner, or stronger. For this reason, we can neither artificially, nor in the various stages of life, acquire any influence on the strength of the after-growth, other than *during the period of new formation or rejuvenation of the deeper part of the follicle.*

From these, I believe clear and generally recognised grounds, it is however evident, that it makes a great difference whether at the time of birth the fine papillary hairs of the embryo remain undisturbed, and simply continue to grow very gradually with the general growth of the subject; or whether, by the general loss of all the hairs, an opportunity is provided for total or partial so-called baldness (*i.e.* in the lanugo stage). In the latter case there are two possibilities which should especially interest us. Either the young epithelial processes are thickened immediately after birth, and in every casting of the individual hair, up to the time of puberty, *but only on the head*, then we have the normal naked human skin; or they undergo this *hypertrophy* on *the whole body*, in regionally varying degree, and then there develope hairy men, showing true, general Hypertrichosis. For in this case,

there only developes, more universally, that condition which, with sexual maturity, appears locally, and which occurs in other pathological changes, in heterogenic, heterotopic or heterochronic manner (Bartels).

That the first really occurs is proved by Geyl himself.

> He observed a girl who was born in February 1885 with long, thick scalp hair, and very well developed lanugo on the rest of the body. This condition did not alter up to September 1887. Then first the points, and gradually all the light coloured hairs of the arm became dark, thicker, and longer. Similar areas of stronger hair developed on several regions. The hair of the scalp reached abnormally low down on the forehead, and passed quite gradually into the lanugo of the face.

In this thoroughly investigated case, there was not only an arrest of the whole hair-change before birth, but it did not appear subsequently, as it frequently does; and individual regions of the embryonic hair gradually darkened and thickened, while as a whole it grew to an abnormally long lanugo. In my view, there was here a true arrest in development; for the generic human tendency to complete nakedness (lanugo formation) before birth was delayed. But it is not excluded that this arrest of development, as Geyl has it, is also a form of atavism. Only there is this important difference in the classification of this form of hair-growth as atavistic, or as an arrest of formation, that for the latter theory there are, in certain cases, histological proofs; while the theory of atavism—which I do not intend to contradict—does not get beyond conjecture, unless one could find the affected ancestor, and observe the development of his hair.

But if this form of excessive growth exist—and I believe that every careful physician will have observed cases similar to that of Geyl, if less developed and more localised — it must be separated from others of adult, universal Hypertrichosis, which appear demonstrably on the altered hairy parts. There is a certain paradox in the description of an excessive production of hair as an arrested formation, which perhaps hinders its adoption; so I prefer to describe the simple persistence of the fœtal hair as "hair stagnation"—Trichostasis,* and thus to separate it from the true Hypertrichosis. The primary object should be, in cases similar to that of the Russian hairy men, to follow the behaviour of the hair from birth, microscopically and macroscopically, in order to determine its position.

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Geyl, Notes and Ideas on Hypertrichosis. Mon., X. Erg.-H.

* Stasis in the sense of arrest, crowding, stagnation, accumulation; Trichokolysis might also be used.

2. Stagnatory tumours.

(a). *Hyperkeratosis universalis congenita.*

A congenital excessive firmness of the whole horny layer, leading in most cases, even in utero, to marked disturbances of growth of the cutis and all underlying parts, and to the death of the embryo; in slighter development, at the time of birth or soon after, to slight but very regular, characteristic changes of the skin, especially at the mucous orifices, without influencing viability.

The earlier cases were all mixed up with Ichthyosis; and unfortunately this confusion still exists, although after Lebert's monograph on the keratoses, the independent nature of the affection, and its near relation to other congenital keratomata (Cornu) were recognised; and Kyber, in his careful examination of one case, determined its position correctly by the name: *universal, diffuse, congenital Keratoma.*

In the most marked cases (works of Hebra, drawings of Kyber's case, see Mon., 1883, p. 207), it affected premature children, who usually died a few hours or days after birth, on account of the impossibility of nourishing them. They were covered all over the body with firm, flat, horny plates, a quarter to a third of a centimetre thick, which burst with the pressure growth of the underlying soft parts, and showed broad, reddish, flat furrows between them. These are only covered by a very thin prickle layer and horny layer, and show no papillary body and no hair follicles. Where the pressure of internal growth is most marked, about the nose and ears, there are deeper fissures into the cutis. All the mucous orifices, especially the eyes and lips, are ectropic, the thin cutaneous plates at these places (eyelids, external ear, nose) have not completed their development, and the entrances are, some of them, covered with horny shields. Where the longitudinal growth is greater than the circular, as on the extremities, the fissures run horizontally, *i.e.* they form rings round the extremity. Where there is simply the one pressure, of underlying organs (nose, mouth, eyes and genitals), the fissures of these regions are circular. Otherwise they have an irregular course, but always at right angles to the axis of the main pressure of the underlying tissue. The horny plates thus cover the whole skin, without any reference to the flexor or extensor surfaces, which in Ichthyosis of adults play such a rôle. Indeed the palms and soles, which in Ichthyosis are always free, are the seat of specially thick ($\frac{1}{2}$ cm.) horny callosities. The hairs of the scalp penetrate the horny plates there, but are long, and correspond to the embryonic hairs of the head, before the change at birth. On the rest of the body, the lanugo is very stunted, and often altogether absent. The fingers and

toes are arrested in development, as are the carpal and tarsal bones, so that the extremities end with clumped hands and feet. Remarkable examples of extreme hyperkeratosis congenita are seen in the cases of Lebert, Kyber, and Jahn.

The slighter forms of this hyperkeratosis show more individual differences, but they have all in common the characteristic retraction of the skin at the mucous orifices. The children are usually premature and immature. The ectropic, shrunken lids only partly cover the eyes, so that conjunctivitis and keratitis soon develope. By closure of the eyes and ears, these organs are also interfered with, so that the children lie senseless, and only show that they are alive by constantly scratching the thickened horny layer. Their survival depends on the possibility of nutrition, for the internal organs are healthy. The development of the nose is more or less interfered with, and arrested. The ears are always directed backwards, firmly pressed to the scalp, and usually only the under part stands out. The skin of the face is very thin, and covered with thin, papery scales. The lips are deformed, the mouth is more or less rounded, but cannot be completely closed. The skin on the body and the extremities is everywhere covered by a thickened horny layer, rough, scaly, and usually dark in colour. Fissures only appear around the joints; here and there there is a development of horny shields, and consequent areation of the surface. This occurs almost invariably on the forearms and legs, where the horny shields surround the limbs like garters, between which the skin with its finer horny layer projects; and after the fall of the shields there first appears a smooth, thin horny layer, which very soon again produces thick scales and shields. Under the pressure of the horny layer, the development of the toes is arrested, the fingers are claw-like at the ends, with stunting of the terminal phalanges and ungual plates, and the nail-bed produces gryphotic horny masses. The whole skin is dry, but baths usually cause sweating. The fatty cushion is regularly atrophic, and the skin may be raised, like that of old people, in thin folds. Only exceptionally, if the children live, is there developed a fatty cushion. In spite of the mobility of the skin, it is, as a whole, too small, and the limbs are usually held flexed, although the joints are freely movable. The musculature of the extremities is also badly developed. Seligmann, Caspary, Behrend, and Lang note examples of slighter Hyperkeratosis congenita.

If the hyperkeratosis, as is very probable, appear simultaneously on the whole surface of the body, we have in the different periods of development of the different parts of the body, means of distinguishing about the time of the commencement of this monstrosity. Certainly the development of the horny covering is the more marked, the earlier

it has commenced in embryonic life. But even where the retraction and the compression of the skin by the unyielding horny covering is only evident soon after birth, the cases are different from Ichthyosis, which begins, at the soonest, in the second year of life. Certainly those cases (*e.g.*, that of Lang) do not, as Caspary suggests, basing his conclusion only on the thickening of the horny layer, represent transitions from Hyperkeratosis universalis congenita into Ichthyosis.

In Hyperkeratosis congenita, the horny layer is not only thickened, as is that of Ichthyosis, but it is also abnormally firm and unyielding, and therefore too small for the body. To these factors are due the contractions and ectropia, which are unknown even in the severest degrees of Ichthyosis.

Ichthyosis shows, like the parasitic epidermic catarrhs, perfectly definite regions of predilection; it prefers the extensor surfaces, and in general spares the flexors, never affecting the palms and soles, and rarely the face and neck.

The ichthyotic Areas are always dry, and it is difficult to induce sweating. In Hyperkeratosis congenita, the Hydrosis, in spite of the horny armour, is normal. The Anidrosis in Caspary's case is exceptional.

The follicular apparatus of the skin in Ichthyosis is normally developed, but plugged; in Hyperkeratosis universalis, atrophic or absent.

Ichthyosis is now and again spontaneously recovered from in the course of infectious diseases, and is endemic in certain regions; this is unknown in Hyperkeratosis congenita.

That only which is common to these fundamentally different processes, and at once distinguishes the hyperkeratosis from the keratoma, is the *diffuse distribution*; but this alone cannot prove the identity of the processes.

In addition to these clinical differences, there are histological ones, shown by the following mutually corroborative results of Lebert, Jahn, Kyber, and Caspary.

These authors all recognise as the main point, *a diffuse hypertrophy* of all the surface epithelia and of the coil glands, along with more or less well marked general hyperkeratosis of the former. We may regard this excess of surface epithelium as a generalisation of a condition which normally appears, sometimes even in fœtal life, only on circumscribed definite areas of the skin—namely, on the palms and soles. As in these situations a complete absence of follicular apparatus accompanies the excess of surface epithelium, and as elsewhere the development of the hair (as in the scalp) is in direct proportion to that of the surface epithelium, Hyperkeratosis congenita

is always accompanied by a diminished development of the cutaneous follicles and the sebaceous glands. The young epithelium, abundantly as it is produced in the embryo, is completely used up by the hypertrophic surface epithelium, and there is only slight development of hair. In many places the lanugo is completely absent. This appears to me to be a more likely explanation of the absence of hair and sebaceous glands than that given by Kyber, namely, pressure atrophy. There are never found, clinically nor histologically, symptoms of plugging of the follicles (horny papules, expressible, comedo-like plugs). That this scanty development of follicles is accompanied by a slight development of sebaceous glands, is only to be expected, in view of their developmental connection.

Equally characteristic of hyperkeratosis congenita as this congenital atrophy of the follicle, is the excessive development of the coil glands, noted by all authors; for as the sebaceous glands provide the fat for the hairs, so do the coil glands that for the epidermis. Kyber and Caspary, whose observations are among the best, found the coil glands extraordinarily large and abundant (see the drawing of Kyber's case, Mon., 1883, p. 301). The ducts are in the form of elongated spiral sweat pores, and may be followed through the thickest horny plates—a characteristic difference between these horny shields and the horny callosities induced by pressure.

The hyperkeratosis, according to the careful description of Caspary, is a *thickening of the basal horny layer*, which, on the portion of abdominal skin examined, contained no fat (was not blackened by osmic acid). The middle and terminal layers are also thickened, though not to such a degree as the basal horny layer. The granular layer is normal, the prickle layer moderately widened. In the absence of any deep prickle layer corresponding to the follicular depression, I would lay no weight on this slight increase of the prickle layer on the surface; Kyber found no increase of the prickle layer. We should then only have to do with an *abnormal distribution*, not with a special hypertrophy of the surface epithelium. The more closely connected surface epithelia show however a firmer connection; only thus can be explained all the other appearances,—the greater width of the basal horny layer, its delayed transformation into the central horny layer, and the piling up of this and the terminal layer. The following symptoms were also noted by these authors: enlargement of the ridge system of the epidermis, and corresponding deformity of the papillary body (sometimes flattening and widening, sometimes elongation of the papillæ), which are to be regarded as due to the influence of the hyperkeratosis on the rapidly proliferating embryonic prickle layer.

While the epidermis and its appendages go through the most multiform changes, which, though not exactly progressive in nature, terminate in the appearance of hypertrophy of the epidermis, the cutis and sub-cutis appear in slighter cases to be normal, and in the severer ones simply atrophic. Caspary found the panniculus feebly developed, the cutis very thin, consisting of fine collagenous fibres, and a scarcely recognisable elastic net. Equally slight is the development of the smooth muscles and the arrectors, which also corresponds to the aplasia of the follicular apparatus. The development of the vascular system of the cutis and the hypoderm is evidently arrested.

If we reflect on the coarse mechanical changes which are induced at the mucous orifices, the ears, and genitals, simply by the pressure of the unyielding horny layer on the underlying soft parts, it appears probable, that in the arrested growth of the mesodermal constituents of the skin, we have only to see a result of the limitation of space on the surface.

Thus all the histological phenomena may be ascribed to one cause, viz., *to a firmer connection* of the epithelium, mainly limited to the surface; as also may the clinical, for even the constant itching is explained as the result of the limitation of space, and the pressure beneath the horny armour.

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(b). *Cysts.*

α. Dermoids.

The dermoid cysts of the skin are, like those of the internal organs, rounded, soft, solitary, yellow, growing, painless, non-inflammatory tumours. They are seated, like the atheromata, always subcutaneously, and show no indication of an opening. From the atheromata, they are distinguished by their appearance in youth, by their topography and by their contents. Their seat of predilection is the vicinity of the root of the nose, and the temples (in the atheromata, the hairy scalp). The neighbourhood of the fœtal fissures has an undeniable influence on their position. They contain, in addition to horny masses and clear fluid, masses of hair; their walls show the structure of the cutis, with hair follicles but also cartilage, bones, and teeth.

Pathologists are agreed in recognising dermoids of the skin as late developed fœtal germs, which have their foundations laid in an early embryonic period, by the wandering of a part of the epidermis into the subcutaneous tissue. They only differ as to the details of the planting of the epidermic germ, and beyond doubt, for the different kinds of Dermoids, we must assume different methods of transplantation. The variety of the contents of the dermoids makes it generally necessary to assume a very early deposit of the germs; at all events, they must be regarded as less differentiated than those germs which are snared off at a later period, and grow into the more simply formed Atheromata. Possibly the circumstance whether only hair follicles and sebaceous glands, or in addition to these, coil glands, are present, may help to decide the period of snaring-off. The greatest difficulty is in the determination of those Dermoids which, in addition to hair follicles, contain bones and teeth, and in which there must manifestly be more than a simple snaring-off from the surface.

A thorough dermatological examination of the dermoid cysts, which has not yet been made, promises to aid in explaining this. Since the constituents of the skin (follicles, coils, elastic tissue, fatty tissue) develope at different stages, the investigation of a large series of differently developed dermoids should decide whether they can be placed in a new series, according to the nature and development of the enclosed organs or not. In the former case, the theory of fœtal inclusion would have to be proved, by the recognition of the agreement of the dermoid development with the embryonic development, histogenetically and topographically.

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β. Atheromata.

These are subcutaneous, indolent tumours, from the size of a pea to that of a walnut, which distend the skin semispherically, show no opening, and contain a gritty, glittering, odourless debris of horny cells. Most of them occur on the hairy scalp. Here they develope slowly, in adults, are often multiple, and show periods of active growth, alternately with periods of arrest, which may last for years. All sebaceous cysts which are seated in the cutis show an opening, and without being pricked, from time to time discharge their contents, as also do those which appear singly on certain parts of the body (face, trunk, extremities), or in areas (genitals), and which in the great majority of cases are not identical

with the true atheromata of the scalp, but are sebaceous or horny cysts, of some other origin. Closed or open cysts which have contents, fatty or smelling of fatty acids, are never atheromata. Only if we clinically fix the definition of atheroma narrowly, and thoroughly examine, microscopically, other structures which clinically in any way differ from it, will it be possible to decide the difficult question whether there are true atheromata, which have an opening and are localised inside the cutis.

Up to a few years ago, in spite of their clinical peculiarities, Atheromata were regarded both by dermatologists and surgeons as simple follicular cysts, or more rarely as sebaceous cysts, although nothing is easier to prove than that the typical atheromata of the scalp contain no sebaceous cells. Then the balance swung round: Franke, Török and Chiari abandoned the view of the atheromata as retention cysts of the sebaceous glands, and showed, though in somewhat different ways, that they were to be regarded as the products of embryonic enclosures, as congenital tumours in Cohnheim's sense. If E. Veiel (Ziemssen) was able to say, in 1884, "that the atheromata develope in the same way as comedones and milium, is beyond doubt," we may to-day say: "that the atheromata do *not* develope in the same way as comedones and milium, is beyond doubt." But in spite of the agreement of recent authors in abandoning the sebaceous gland hypothesis, there is still a good deal of obscurity in exactly defining the atheromata from other congenital tumours (Dermoid) on the one hand, and from certain acquired horny cysts on the other, and greater caution in clinical diagnosis is desirable than is usually observed.

F. Franke was the first to shatter the old doctrine of the sebaceous gland origin of atheromata. Then Török further confirmed the new theory of embryonic ensnaring of atheroma germs, by a detailed histological investigation of the walls and the contents of the atheromata. Franke only worked with alcohol preparations and sections; Török used osmium and surface ones as well. He confirmed Franke's observation of papillæ in the atheroma walls; of nine atheromata, seven contained more or less large papillæ, and a well-marked ridge system, like the surface epithelium. On the other hand, osmic acid showed almost invariably an absence of sebaceous cells, and of fat generally; only in one atheroma of the hairy scalp, were there found nucleated cells, which with osmium showed blackened drops; and in an atheroma from the forehead of a man of 56, the atheromatous nature of which was doubtful, there was a good deal of free fat, and at the same time the remains of a cutaneous follicle with an adherent arrector muscle. Even Török's two "cutaneous atheromata," which had openings, and which, to my mind, were doubtful specimens, contained no fat. The contents consisted of concentrically arranged horny layers, plates of cholestearin, and the debris of both constituents, with the frequent addition of

fragments of lime and pigment. These represent the typical contents of atheroma.

Török lays much weight on the almost invariable occurrence of a papillary body in the wall. As a fact, it appears probable that a follicular retension cyst, which is developed by extension of the follicular walls, would not show in its walls, at a later stage, any regular papillary body; while after the descent of a fragment of the cutaneous surface to a deeper level, such a body might remain retained, and thus appear as a witness that the atheroma epithelium represents an enclosed portion of surface epithelium. In this sense, the work of Török is certainly of great value, and an investigation of the atheromatous-like structures will never in future be complete, without the investigation of the walls on sections made horizontally. In view of the well-known variability of the papillary body, we must not, however, jump to the conclusion that a strict line may be drawn from the existence of this structure. But if, in further repeated investigations, it were confirmed that all atheromata in the strictest clinical sense of the word (especially the typical subcutaneous closed atheromata of the scalp), always, at least in the early stage, showed a well-developed papillary body, and the follicular cysts never, then we might use this criterium as a distinction; for the investigation of the papillary body on cross sections is always simple and sure. But a *necessary* relation between the atheromata and the papillary body, no more occurs than a *necessary* mutual exclusion of follicular cysts and papillary body. The former, Török does not assume; in two of his cases the papillary body was absent; but it might have been, as on the surface of the skin, flattened out under the abnormally high pressure. The follicles, on the other hand, tend very much to the production of epithelial buds, and when such a follicle expands, there must develope, at least here and there, a ridge system. Therefore Török says: "We cannot assume that a papillary body or a ridge system, of the *extent* and *regularity* which is so often found in the atheromata, could be developed at the dilated orifices of the follicles." But we have seen, in considering follicular cysts, that even on their follicles, a flat, widespread papillary body may very well secondarily develope, if the epithelium grow; and that one often finds, on one side of such a cyst, a papillary body, while on the opposite side, the margin between the follicle and cutis is quite flat. And this supplementary papillary formation is not remarkable, for we must assume, on account of the constant enlargement of the cyst, a constant proliferation of the follicular epithelium, and this prickle layer cannot extend towards the inside of the follicle. It must, then, seek to enlarge outwards, and therefore it grows into the cutis.

Whether this ingrowth is entirely concentric, or takes place in the form of a ridge system, with preservation of the papillæ, will depend in each case on whether the external resistance is regular or irregular. It is of course very regular, if a very firm follicle membrane is formed; irregular, if a delicate, loose membrane surrounds the expanding prickle layer. For atheroma, however, these relations are exactly the same as for the follicular cysts; and while Török has shown us the wide extension of the papillæ and ridges in the atheroma wall, that in my view only shows, that here, as in the follicular cysts, the secondary formation of a papillary body is possible. The view, that in the papillary body of the mature atheroma, we have the same papillary body which belonged to the ensnared piece of the epidermis, I cannot admit; for the scalp, where the typical atheromata occur, shows either a very feebly-developed papillary body or none at all. Further, I believe that every papillary body is too temporary a formation to share in the process of elongation, and the excessive later extension, without undergoing change of form. I believe that every atheroma, like every follicular cyst, can, by epithelial growth, provide for itself a new papillary body.

But while I do not see in the frequent occurrence of the papillary body in the atheroma wall, a proof of its origin from the surface, and in the demonstration of it in individual cases, do not recognise the feature which permits the distinction of atheroma from the follicular cysts, I still agree with Török in his conclusion, that the true atheromata are a sort of simple dermoid, and are developed from embryonic aberrant germs. But I limit at the same time the definition of atheroma to the familiar subcutaneous, enclosed cases, such as occur on the scalp. In this limitation I agree with Franke and Chiari, only that the former assumes not an ensnaring of the whole skin, but merely of the surface epithelium, and prefers to call the atheromata "Epidermoids," in contrast to "Dermoids." Chiari definitely distinguishes the large, deep-lying atheromata from the follicular cysts, as true dermoids.

Histologically, then, Atheroma is to be defined as an epithelial collection, cornified in the centre, and lying in the hypoderm, which is margined from the surrounding tissue by a firm or delicate connective tissue capsule, and gradually leads to atrophy by its pressure on the adjacent constituents, especially the follicles above it. The membrane shows no sign of inflammation, and contains few vessels and cells; usually it is less well-marked towards the surface than beneath and at the sides. The older the atheroma, and the firmer its walls, the more distinctly is it margined; and the atheroma lies with its firm horny contents, which preserve its form, almost free in the hypoderm. The prickle layer of the follicle forms a level surface towards the connective tissue, or may show ridges with papillæ between. The prickle layer is

usually from four to eight layers thick, and the cells show distinct fibrillation. It usually passes, owing to the high internal pressure, without any granular layer, directly into the horny layer, which consists of thin, compressed, usually anuclear cells. We often meet patches of granular cells, as well as eleïdin in the horny cells, and often patches of nuclei in the horny layers. Towards the centre, we find cholestearin between the horny cells, corresponding in amount to the age of the atheroma and the degeneration in the centre. Thus develope brittle, amorphous masses, which are to be regarded as the broken down remnants of complete, welded horny accumulations. Probably under the higher pressure in the centre, the cholestearin of the horny cells separates from their albuminoid constituents. These amorphous remnants tend to liquefaction. The older, larger atheromata therefore alone show the debris-like contents which give the tumour its name; they are doughy and kneadable. Where this central degeneration does not occur, the atheroma is a firm, purely horny structure. Very old atheromata sometimes take up calcareous salts, and then show hard areas or a hard shell.

Whether in the true atheromata, hair follicles and sebaceous glands occur in the walls, is a question which I prefer to leave undecided. Impossible it is not, and if we reflect on the near relation of the atheromata to the dermoids, it is almost to be expected. The numerous discoveries of hair and sebaceous fat in the atheromata do not refer to true atheromata, any more than do those of Török (cases 9 and 13). And the long familiar and much discussed relation of sebaceous cysts to papillary acanthomata, cutaneous horns and cancers, must be anew investigated, bearing in mind the sharper definition of the atheromata.

Should it be made clear that the atheromata in the narrowest sense of the word never contain follicular structures, there would be no ground for not separating them—as has clinically often been attempted—from the other dermoid cysts, and Franke's name, "Epidermoid," would be to a certain extent justified.

The atheromata are easily distinguished from all horny and sebaceous cysts, by the absence of an opening, and from the latter, further, by the very different contents. Further, an important factor separates them (together with the dermoids) from all follicular cysts, namely, the *absence of Micro-organisms.* I must lay much weight on this fact, for by it alone has it been possible for me to distinguish certain very atheromatous-like, large follicular cysts, from true Atheromata.

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(c) *Pigment Nævi.*

It is more on theoretical than on practical grounds, that the pigmented nævi are here referred to as a special class of stagnatory tumours. Practically, the pigmented nævi are almost all soft nævi, and we have already discussed them. We have further seen there the intimate connection between soft nævi and pigment, and learned that pigmentation definitely favours the metaplasia of the surface epithelium to non-fibrillated epithelium, and therefore the dispersal of the epithelia, which is in the nature of the soft nævi.

Were there no other pigmented nævi than the soft ones, they would only form a subsection of the soft nævi. But there are, in the first place, areas of skin, which clinically appear as small, dark brown, isolated, pigmented moles (Lentigines), and which microscopically show no formation of epithelial nests; and there are, exceptionally, hard pigmented nævi—even without epithelial dispersal. Certainly out of twenty small pigmented nævi, I have only found one without epithelial nests, and only one pigmented hard nævus. But these cases suffice to show, that pigmentation is not necessarily connected with the soft nævi. It is, as a fact, not easy to see why the melanotic pigmentation of an epidermic area, or of a hard nævus, should in every case lead to epithelial scattering, for inside the pigmented nævi, there are many pigmented epithelial areas, without simultaneous metaplasia and growth. On these grounds, a class of pigmented nævi is necessary. How often pure cases of pigmented nævi occur, remains to be investigated.

Literature—see under Nævi.

Nævi seborrhoici (*Seborrhœic warts*).

These are multiple, papular, flat elevations, usually oval in form, and in size from a lentil to a bean, sharply margined and of a yellowish colour, tending to grey or black. They develope slowly, in adults, usually in elderly persons. The smooth surface is covered with black points, corresponding to the follicular openings, or with a greasy, black, firmly adherent scale or crust. They are seated usually on the seats of predilection of seborrhœic eczema—the interscapular and sternal regions—then on the neck, abdomen, and elsewhere on the trunk. In younger persons, one can sometimes see the first commencement, as faint, yellowish, smooth, somewhat elevated spots, without black points; such persons are usually the subjects of seborrhœa. They cause itching only in older persons when they rapidly increase in size. They may be elevated as much as two millimetres over the surface, and run together into large plaques. They never disappear spontaneously. They are described by Neumann as senile warts.

The histological descriptions of the affection differ very widely.

Neumann found the prickle layer thinned and pigmented, and the cutis atrophic, with pigmented vascular sheaths. The hair follicles were cystic, and filled with fat and hairs; the sebaceous glands were hypertrophic, and also converted into cysts, which reached over the surface of the skin.

Balzer found the prickle layer markedly hypertrophic, the granular layer and stratum lucidum normal, the horny layer somewhat thickened, the papillæ markedly enlarged and irregular, the cutis normal, and only a slight increase of nuclei along the vessels.

Handford also found the prickle and horny layers markedly thickened. These contained numerous round spaces, whose walls are lined with cubical or elongated cells.

While thus, according to Neumann, there is a follicular cyst formation in senile atrophic skin, Balzer and Handford found the surface epithelium atrophic, and no cystic changes in the follicles. But they all agree that the cutis is normal, and the affection is thus mainly epithelial.

On the other hand, Pollitzer, to whom we owe the best description of the affection, comes to the conclusion, that important changes occur in the cutis. He found the papillæ elongated by epithelial growth, and filled with large, nucleated "epitheloid" cells, which extend from there to beyond the sub-papillary vascular plexus, and end abruptly underneath it.

"These cells show indications of a definite arrangement in groups, and in straight and bent lines along, and parallel to the capillaries. This arrangement is most clearly seen at the lateral parts of the section, where the cell collection is less dense, and one sees here also, that the cell growths are separated from one another by connective tissue bundles." The blood vessels, elastic fibres, and sebaceous glands, are normal; mast-cells are present in abundance. The follicular orifices are plugged with horny substance, and the horny layer at different places descends downwards. The prickle layer, especially the inter-papillary, is markedly hypertrophic. In the centre of the tumour, the ridges are thrice as long as in the healthy surroundings. The horny layer is parakeratotically altered (shows deficient formation by the cells of keratin), nucleated, which Pollitzer incorrectly attributes to a want of drying, induced by the covering with sebum. The upper layers of the horny layer of the surface, as well as of the follicles, contained foreign bodies and dirt. The sweat pores are cystically dilated, to ten times their normal diameter, by plugging of their openings, and in the cysts are found degenerated epithelia, along with leucocytes. Pollitzer regards these poral cysts as probably identical with Hand-

ford's spaces. The lumina of the coil glands are markedly dilated, and the epithelia contain a greater quantity of fat drops than normal. Fat is also found free in the spaces of the cutis and the papillary body, and is especially abundant in the inter-spinal spaces of the prickle layer, especially at its deeper part.

Pollitzer mixes up much that is valuable with matters that do not belong to the tumour under consideration. The material he examined was evidently of a mixed nature, comprising, among others, seborrhœic warts which came from a case of Mycosis fungoides, under treatment in my clinic. Some of the symptoms which he found—the fat in the cutis, in the surface epithelium, and especially in the coil glands, as well as the occurrence of peculiar "epitheloid" cell nests in the papillary body —are indeed characteristic of the Nævus seborrhoicus. They make it possible for Pollitzer to determine the whole character of the tumour as a Nævus. But other symptoms—the marked widening of the prickle layer, the parakeratosis of the horny layer, the cystic formation of the sweat pores, the marked accumulation of leucocytes and mast cells, and (as I can add after examining the preparations) plasma cells,—all these symptoms are those of the contemporaneous Mycosis fungoides. Just because Pollitzer's description is half right, I cannot pass over the incorrect portion in silence, without risking the transmission of error into future literature.

After I had recognised the part played by Mycosis fungoides in Pollitzer's material, I had eight opportunities of examining seborrhœic nævi from the dead subject, in osmium and alcohol preparations. Since all these eight cases show a sufficient similarity, I believe I am at last able to point out the right position of this much discussed growth. I found, briefly, that the seborrhœic warts are really true *soft nævi*, which are only distinguished from ordinary soft nævi by their containing *more fat*. If one examines half of such a tumour, in alcohol preparations, it is difficult to draw any distinction from an ordinary soft nævus. Down to a certain depth extend the epithelial nests, and they are, as usual, divided up by small, deeply-penetrating epithelial ridges, sometimes still in connection with the nests.

In the middle of the cutis, or somewhat higher, the border of the epithelial nests tends to be marked off horizontally, and from here, to extend to the surface epithelium in almost equal breadth. The seborrhœic nævi differ from the ordinary soft ones in this, that the one has a flat form, the other in general a more septate arrangement of the epithelial nests, and thus the former usually have a flatter form than the latter. In addition to this slight difference in the structure, it should perhaps also be noted, that in the seborrhœic nævi the loops of the coil glands are broad, the epithelia very large and clear, and that they show a

particularly broad, clear external zone, while the nuclei are all directed towards the lumen.

Otherwise everything is the same as in the soft nævus—the absence of elastin at the seat of the epithelial nests, the presence of mast cells and pigment, the accidental implication of the hair follicles in the epithelial growth, and so on. The same nævus looks very different in osmium preparations. Here we find all the seborrhœic symptoms noted by Pollitzer. The most remarkable of these is the presence in the coil glands of large fat drops. These drops were present in every-one of my sections, and this is a remarkable proof of the production of fat by the coil glands, which Meissner and I have pointed out with such little result. Then we find the fat scattered in drops in the cutis, and much more abundantly in the surface epithelium, and the adjacent papillary body. Sometimes we might almost speak of an injection of the lymph spaces with fat, for the appearance is just like that of many pigmentations of this region. That these black masses are fat and not pigment, is shown on the addition of $H_2 O_2$, which leaves the slight pigmentation undisturbed. I have only to add, that even epithelial nests sometimes contain fat. Here, as in the surface epithelium, rows of very fine (black) fat drops surround the individual cells, and even shroud them with a black veil. The amount of fat in the epithelial nests varies very much. Where there is not much fat, it is only found in the superficial nests, which lie directly on the surface epithelium; where it is more abundant, all of them may contain it. In several of my seborrhœic nævi, the osmium preparations, and these only, show a coarse fissuring of the epithelial nests, some of the balls being separated from the rest of the nævus epithelia, by the formation of wide lymph spaces. It appears as if a special fatty degeneration of the epithelial nests occurred. But comparison with the corresponding alcohol preparations shows that the gaping spaces are to be set down to the action of the osmic acid, and that the occasionally appearing coalescence of collections of epithelia into larger balls is the same appearance which is found, sometimes without, sometimes with simultaneous pigmentation, in non-seborrhœic nævi. Just like the pigment, the fat collects mainly in the lymph spaces of the surface; there is thus a broad analogy between the infiltration of pigment and the infiltration of fat in nævi, between the Nævi pigmentosi and the Nævi seborrhoici.

That all seborrhœic warts are only *seborrhœically degenerated soft nævi*, I will not definitely say, in spite of the accord of my eight cases. For it seems to me very remarkable, that Neumann, Balzer and Handford have published such very different results. It is possible that other forms of nævi, hard or follicular, may become seborrhœic. But

in future, any so-called senile or seborrhœic warts, which show such a different histological appearance, must be very carefully tested in regard to the clinical diagnosis.

LITERATURE.

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(e). *Nævi angiomatosi, Elephantiasis congenita angiomatosa.*

The almost entire limitation of the congenital angiomata to the superficial layers, would seem to point out that they are developed by the action of some external cause. Yet it is in these growths, more than in any others, that the theory of maternal impressions has acquired a special prominence. Even in apparently authentic cases of this nature, we are obliged to assume the intervention of some functional nervous disturbance, quite beyond proof or discussion; and Virchow was the first to indicate a possible anatomical cause, namely, a connection of the embryonic fissures of the skin, especially the branchial fissures, with the appearance of angiomata at their areas of predilection (eyelids, cheeks, ears, nose, lips). Thus he names the angiomatous nævi which occur in these parts—" fissural angiomata." According to him, " a very slight irritative condition at the borders of these fissures, which are very abundantly supplied with vessels, is sufficient to induce a greater vascular development, which might possibly be recognised as a nævus, but which remains latent and only later becomes manifest." This hypothesis, although everywhere quoted, is not much adopted by recent authors. It deals only with a possibility, which in the regional concurrence of the nævi with the branchial clefts has a certain air of probability; but a basis of fact, by the recognition of nævi on the branchial fissures of the embryo, it does not as yet possess. We may use Virchow's idea as an adjuvant, without depending on it alone for the explanation of these nævi.

I have long been under the influence of another idea, in which I have only been confirmed by numerous experiences. It was the methodical treatment of Pityriasis capitis, which I introduced into practice in 1881, which showed me that an extraordinary percentage of individuals had a venous nævus in the neighbourhood of the occipital fontanelle, hidden by the hair. The recognition of this nævus, which has since been observed by everyone, was of practical importance; for by nurses it was often regarded as an inflammatory redness, and therefore treated as such, of course without result. With the assistance of

my nurses, I have gathered statistics on the frequency of this one form of nævus, and find that between ten and twenty per cent. of all adults have it, though often only in traces. Some years later, I first noted, in an infant, a coincidence of this occipital nævus with an exactly similar one on the forehead, seated diametrically opposite. In this case, the attribution of both nævi to the action of diametrically opposed points of pressure, during intra-uterine life, was strongly suggested. Since I got this idea, I have investigated all angiomatous nævi of the body, to see whether they would not fall in with this hypothesis of intra-uterine pressure, and the results exceeded my expectations. Even the frequent affection of the head agrees with the fact, that the common position of the fœtus brings the head, and especially the face and occiput, into intimate apposition with the bony parts of the maternal pelvis, in the later stages of intra-uterine life. After the head, it is especially on the hands and feet, and on the trunk, especially the regions of the sacrum and the buttocks, that I have met with venous nævi—all parts of the body which can be demonstrated as points of pressure during fœtal life. The preponderance of left-sided nævi of the face in my observations, corresponds to that of the first position, if one regards as the main point of pressure, the maternal promontory, in the erect position. In contrast to Virchow's fissural theory, and the less grounded nerve theory of Th. Simon, the pressure theory fits all those cases of wide-spread angiomatous moles which are irregularly broken up by normal areas of skin, and have a quite irregular margin. For the affection of a nerve branch from a central cause, or of a branchial fissure developmentally, requires a certain continuity of the nævus, and an approximately regular margin. Such a regularity is, in my experience, quite exceptional. And more frequently, I found these moles margined by the bony prominences of the skull, which are present in the fœtus, as the eyebrows and back of the nose, chin and lower jaw. The unilateral position of many of these moles, used as an argument for the nerve theory, is too inexact to be distinctly related to certain nerve-areas, but quite exact enough to correspond to the unilateral pressure of a maternal bony-angle on the bony prominences of one side of the fœtal face. That many less prominent points must escape the pressure is evident, and this would explain the irregular form and the discontinuity of many nævi. But the strongest proofs of the pressure theory are found in those cases in which neither branchial fissures nor nerve-areas can have anything to do with the case. These are, firstly, those cases in which opposite regions of the body are affected by circumscribed nævi, such as that mentioned affecting the forehead and occiput. I have further noted an occipito-facial and a sterno-scapular case. In a second category are those nævi which, though apparently far apart, are brought

very near by the intra-uterine position—*e.g.*, face and outer arms, ankles and buttocks. Thirdly, there are those cases in which the nævus is certainly unilateral, but absolutely contradicts the nerve theory by overleaping a wide area of skin. Thus, I recall a widespread nævus of the buttock and the outer side of the thigh, which consisted of two parts, with an almost linear interval; and a nævus of the face, which extended from the lower jaw directly to the eyebrows, and some points of the nose and upper lip. Such cases are explicable neither by the fissural nor by the nerve theory, but only by the pressure theory.

But if this pressure theory be correct, the question is: how does the pressure act? This may be in different ways. Either we may assume a stagnation of the blood in definite regions of the skin, produced by peripheral constriction, analogous to the venous stagnation of the leg by pressure on the pelvic veins in pregnancy. This pressure must not be too great, but it must affect the whole area. These conditions are not found in most nævi, and are at most to be assumed in those which affect a whole hand, a foot, some part which can be completely ensnared, *e.g.*, by the umbilical cord. Or one might explain the pressure by assuming that the blood is at first pressed out of a region of skin, and thus the vessels paralysed. Such a pressure anæmia is followed invariably, in extra-uterine life, by a prolonged paralytic hyperæmia, the arrest of which depends on the integrity of the tonic ganglia. The more these are injured by the pressure, the longer does this congestive hyperæmia last. This action of pressure appears to me to fit in with the conditions of most nævi. For its production, we have to consider the adjacent bony angles of the maternal and fœtal bodies, and the inter-dependent pressure of the infantile limbs. There are of course other general factors to be considered—the size and form of the maternal and fœtal structures, the amount of liquor amnii, the number of previous pregnancies—all things, the complete estimation of which I must leave to the accoucheur. I will only note that in some cases the mothers of children affected with nævi have stated definitely that they had noted a strikingly small quantity of liquor amnii, and that my cases occurred chiefly in first or second pregnancies. To this last point I have only recently directed my attention.

Assuming that the theory of the relation of venous nævi to local pressure turns out, on further research, to be correct, I believe that by this theory alone can their development be explained, even although we know that the transient pressure which the head undergoes in birth is without any further results on the skin. It is not probable, that in the embryo, the tonic, vascular ganglia play the same regulating rôle

as in adults, for we know that in infants there is a relatively weak vascular tone; and the great aid to the vasomotor regulation of the cutaneous vessels, external cold, is completely absent in utero. Pressure paralysis of the embryonic cutaneous vessels might then very well have as a result, persistent hyperæmia, which cannot be overcome by the weak vascular tone. The persistently dilated and over-nourished vessels must combat the higher blood pressure in some other way; thus, precisely as in adults, where the tone is insufficient, their walls thicken. But since here we are dealing with a raised pressure by blood stagnation, it must be the dilated veins and capillaries which thicken. It seems to me to be a confirmation of the pressure theory, that, as microscopical investigation shows, the angiomatous moles, in contrast to most other angiomata, show dilatation and eccentric hypertrophy of the venous system only.

I have gone into this etiological question more fully than perhaps appears necessary, because I regard the angiomatous nævi as a valuable example of the relation of mechanical disturbances during embryonic life, to persistent malformations of the skin; and because the conditions in other malformations are much more obscure and less open to investigation than these. It is to be hoped that the question will be re-investigated with more abundant material.

The angiomatous nævi usually occur singly, are rarely multiple, only exceptionally scattered over the whole body, are of a fresh red or bluish red colour, now and again dotted with dark red points, and more or less sharply margined from the surroundings. They are at first flat, and remain so; or they gradually fade, and in some cases entirely disappear. In other cases, the skin thickens all over the nævus, or on certain parts, and there gradually appear dark red prominences, which enlarge into pedunculated growths, and may be snared off. When with the diascope we remove the capillary redness, we see a pretty dense net of dilated cutaneous and subcutaneous veins, and inside them larger, blood red points. The nævi undergo these atrophic or hypertrophic changes *in situ*, but they do not invade, like the arterial angiomata, the surrounding tissue; they are not progressive. Certainly one reads in almost all text-books, that the growing angiomata develope on the basis of ordinary flat nævi, but in such cases there is probably a confusion with the first stage of Angioma plexiforme arteriale, for the latter, when extirpated, shows no trace of the type of nævus. Such an insufficiently supported statement does nothing but confuse the important anatomical and clinical differences between the two forms of angioma. My pressure theory of course relates only to nævi proper.

Our knowledge of the formation of angiomatous nævi we owe to Virchow, and in the last thirty years there has not been one single important fact added to his statements. It is rather time to turn back to them, since, by the assumption of a variability of the vascular

character, which does not exist, the clearness which he gave to the matter has been somewhat obscured. What we here understand by simple angiomatous, non-progressive nævus, Virchow described as Telangiectasis venosa, Angioma varicosum simplex, or Nævus varicosus; and he rightly separated it from the other Angiomata.

The dilatation affects mainly the veins of the cutis proper, not the arteries or capillaries, as may be seen with the diascope. The veins, from the hypoderm onwards, do not undergo the ordinary change into thin-walled capillary tubes, but show an irregular, broad lumen, and a wall about the thickness of the smaller subcutaneous veins. Only in the neighbourhood of the papillary body are the walls of the venous capillaries formed of a simple wall of endothelium, and here we have irregular varicose dilatations, and even the formation of thin-walled cystic cavities. The veins of the cutis are also increased in length, and therefore have a more winding course than usual; but we never see the cork-screw-like and anastomosing blood vessels of the ordinary angioma. The arteries too, in contrast to the other angiomata, are normal in calibre and course. We see at once that this form of angioma is of a purely venous type, and that the hyperplasia of the vessels is not indicated by capillary budding, but is a process secondary to an angiectasis induced by stagnation. But we must not regard the venous character of the nævus as the cause of the bluish colour. Virchow rightly attributed the lighter red or more livid colour of the angiomata to their more superficial or deeper position; but nevertheless many recent text-books, among them Kaposi's,* attributes the distinction in colour to the proportion of arteries and veins. This is incorrect. Angiomatous moles are all venous in nature. The colour is simply due to the greater or lesser development of the superficial varices. The more such papillary angiectases project, the lighter red is the colour; carefully examined it is dotted with dark red. The dull, bluish-red, livid, angiomatous moles show the ectasis and hyperplasia of the veins only as far as the upper margin of the cutis proper, while the papillary varices are absent, or very small and scanty. Pieces excised from different parts of two cases show very distinctly this relation of the colour to the more or less superficial extension of the angioma. The circulation of blood in the nævi, even in blue ones, is as a rule accelerated, as may be noted on excision, simply because the vessels are dilated, and the resistance is less. Since the venous capillaries of the cutis

* This gives me the opportunity of pointing out a remarkable error into which Kaposi has fallen (Lectures, Third Edition, p. 740), in ascribing to Virchow the view that the angiomata developed independently of pre-existing blood-vessels, while Virchow was actually contesting this old view of Rokitansky.

have taken on the character of larger veins, we may almost say that here a part of the normal circulation is over-leapt, and the short arterial capillaries pour their blood directly at the surface of the skin, into the veins. So long as the flow of blood goes on without hindrance, the blood must run more rapidly, and show an arterial colour, because the capillary circulation is shortened. Only when artificial hindrances are added, when, for example, the afferent arteries are contracted by the influence of cold, or, by abdominal pressure, the black-flow of the blood made more difficult, as habitually in many nævi of the lower extremities and genitals, do we have a delay of the circulation, and then, merely on account of the greater amount of stagnant blood, an unusually deep blue colour.

In the absence of capillary budding, and the formation of loops, the nævi secondarily show, as a whole, a much greater approximation of the vessels to the normal, than the previously described arterio-capillary angiomata. Their mode of formation is as if all the vessels of the cutaneous veins were fully injected, and the walls of the venous capillaries thickened to the thickness of veins; the number of vessels is only slightly greater than normal.

But when the angiomatous nævi are separated, by these peculiarities, from the other angiomata, and arranged in the simple category of eccentric hypertrophies of the walls, we have, as we see, on the one hand, new support for the pressure theory; and, on the other, the important clinical observation, that they show no tendency to extension, like many other angiomata. I by no means deny that the independently proliferating angiomata may develope on the base of a nævus; and it is very possible, though not histologically proved, that many take their origin from small, unnoticed nævi. But the principal differences of the histological structure, and the clinical appearance of the two forms remain; and such a combination must not induce us to combine all the angiomata, and thus to return to the obscurity from which Virchow rescued us. The angiomatous nævi certainly show, like all nævi, a post-embryonic development, and under some circumstances, a sort of hyperplasia; but this is quite unique in character, and requires special consideration.

I have previously spoken of a thickening of the walls of the venous capillaries in the cutis, which causes them to resemble subcutaneous veins. This resemblance relates only to the thickness, not to the structure of the wall. There follows on a continuous endothelium, a cellular collagenous substance, lamellated in the larger vessels, which passes without any sharp margin into the cutaneous surroundings, and is only distinguished from the last by the deeper stain which it takes with inter-cellular stains. Then the thickness of the walls, so far

as can be established in staining, is developed in different degrees, remaining pretty regular inside the cutis, but becoming reduced, at the seat of certain varicose dilatations, and then very gradually at the border of the papillary body and inside it, to a simple layer of endothelium. Finally, there exists a very important difference between the hypertrophic venous capillaries and true veins, in the absence of elastin in the former. That the dilated vessels, in the embryonic period, contain no elastin, is self-evident, but that in post-embryonic life, when they take over the venous function, they should form much less elastin than the subcutaneous veins, is remarkable, and possibly depends on the former surroundings of these venous capillaries, and their enclosure in the cutis. Up to a certain degree, the fibrous tissue of the cutis bears the brunt of the increased blood pressure; the thickening of the walls is to be regarded as a perivascular condensation of the cutaneous tissue. Certainly the elastin on the veins is never completely absent; in one of my preparations, there is formed around all the larger veins, down to the neighbourhood of the papillary body, a fine, long-streaked membrane, which follows directly on the endothelial membrane, and corresponds to the thick elastic membrane of the subcutaneous veins. In other preparations the elastin is more scanty, and in the papillary body altogether absent, though here the ectasis of the veins is in parts more marked than in the cutis. The surrounding fibrous tissue of the cutis is widely dilated around the blood vessels, and poor or completely wanting in elastin; but it is abnormally dense, rich in spindle cells, and poor in lymph spaces—in short, abnormal. Only the arterial capillaries are of normal calibre and width, and are as usual completely free from elastin.

We see that in the artificially induced, or spontaneous atrophy of the angiomatous nævus, the method is relatively simple. We have not a complete destruction of the new structure, but a simple narrowing and reduction of the hypertrophied vascular area, and it is a mistake to let this malformation alone dominate our idea of its nature. In many cases, the natural development leads also to hyperplastic formations, which require energetic treatment. The nævi appear over the surface of the skin, show multiform and variegated, readily bleeding protuberances, some of which are snared off (angiomata pendula), and are finally converted into elephantiasic, very disfiguring structures. All this usually takes place without any distinct advance of the angiomata into the healthy surroundings.

These hypertrophic nævi, then, really show the new formation of vessels going on beyond the primary ectasis, but in spite of that, no capillary budding. We have rather a thickening, elongation and looping of the whole vascular tract, on the one hand, and a fibroma

formation of the cutis on the other. In the centre of the polypoid protuberances, we meet on vertical sections, on account of the great widening, almost nothing but cross sections of very much dilated veins and less dilated arteries, with a lesser number of oblique and longitudinal segments. Usually three or four sections of veins are enclosed along with an artery in a connective tissue sheath, the elements of which are distinguished by their fainter stain and more distinct fibrillary markings, from the broad cellular rings, consisting of homogeneous collagenous substance, by which segments of vessel-walls are here represented. The whole hypertrophic skin has, in its central and under parts, passed into a plexus of thickened, inter-twining vascular cords, and only on the surface do the finer varicose vessels show the ordinary appearance of Nævus angiomatosus planus. Of four such tumours, two showed further development into a varicose, and even the commencement of a cavernous angioma, losing, in the most markedly dilated veins, their round form, showing dilatations, and in places running together into large, distended cavities. But this transformation takes place only between the veins of one and the same vascular cord, so that this has the structure of an endothelium-clad sponge, while the neighbouring cords still show the individual vessels. The cavernous transformation in the hypertrophic vascular moles appears never to become great, for the tissue is too firm; there occurs, with the vascular hypertrophy, that of the collagenous interstitial tissue also, so that in some places the tumour gives the impression of a fibroma. Since the walls of the thickened vessels pass without any sharp margin into the cutaneous tissue, the share of the latter in the hypertrophy is explicable; for although the flat vascular moles here and there show elastic tissue on the venous walls, the elastin in the secondary growths under consideration is completely lost, both in the vascular walls, which consist essentially of compact layers of collagenous tissue and concentrically arranged connective tissue cells, and in the interstitial tissue. The absence of elastin, along with the expansion of the growing vessels, explains the tendency of the hypertrophic nævi to become pedunculated, the elastin of the surrounding parts pressing them out like knobs. The rest of the cutaneous structures also suffer under the influence of this vascular growth; the follicles are shortened and lost, and muscles and coil glands are pressed aside and atrophied,—symptoms which are absent in the flat vascular nævus. These results are to be regarded as simply mechanical, and induced by the general limitation of space, and by no means as indicative of any special relation of the vascular growth to the several organs of the skin.

If we review the changes of the vascular nævi during extra-uterine life, we find that these also have the general venous character which I

have described as depending on stagnation. The tuberous nævi bear the same relation to the flat, as the markedly thickened and winding varices in the elephantiasic leg do to ordinary varices. On the contrary, the appearances of independent transition into an angioma of arterial capillaries, are altogether absent in my preparations. If such a condition should ever be recognised, it would certainly not constitute, clinically, a pure case of nævus.

From the hypertrophic nævi of adults, it is only a step to Elephantiasis angiomatosa, Angio-elephantiasis (Kaposi). If, instead of the embryonic stagnation in the cutaneous vessels, there are found disturbances of circulation in the subcutaneous and larger trunks, it is easy to understand that hypertrophic appearances in the larger vessels (which otherwise we only see rarely, and as a later development of the flat vascular moles) may be well developed at birth, and may gradually lead to more marked affection of the neighbouring tissue. It is very much in favour of a simple stagnatory cause, that such vascular moles usually make a whole extremity elephantiasic, while the whole body is very rarely affected.

In Rokitansky's case, the whole right arm was converted into a soft, knobbed, bluish tumour, which could be squeezed like a sponge. In that of Pitha, the forearm, especially the hand and the fingers, down to the ungual phalanx, was enormously swollen, and the thinned skin was distended by innumerable soft, elastic tumours, of the size of nuts, and dense convolutions of varicose veins, some of which contained phleboliths. In the case of Lamorier, the whole arm was bluish black, soft, "like a calf's spleen filled with air," but only half its natural size. On elevation, it markedly diminished, while tumours formed on the shoulder and over the pectoralis major. Leisrink observed an Angio-elephantiasis of the right arm and hand. The skin was pale, permeated by a venous net, and distended in many places by bluish tumours, the size of hens' eggs. The hand and arm were larger than on the left side.

In this last case, the largest of the excised tumours proved to be an encapsuled cavernous angioma, whose walls, $1\frac{1}{2}$ millimetres thick, showed an intima, a double muscular layer, and a looser adventitia, and into which a vein, 2 millimetres broad, could be traced. The surrounding tissues showed also a cavernous formation, and a cellular infiltration accompanying the blood vessels.

Similar elephantiasic angiomata have been found on the under extremities. Schuh observed one on a leg, which felt soft and elastic, as if consisting of pouches filled with blood, in which phleboliths were present. The leg was double the size of the healthy one, swelled up enormously on standing, and became tense and blue, without showing individual varicose veins. Smith describes a case in which the leg was affected by large, flat, angiomatous moles and thick venous convolutions, was much larger than the other, and swelled up

when dependent. In another of his cases, the enormously thickened leg was the cause of difficulty in parturition. The whole external surface of the thigh was occupied by a dark-red vascular nævus, and the buttocks by a few small spots, giving on pressure the sensation of a doughy, spongy mass. The whole leg was much larger than the healthy one, owing to a thickening of the skin and subcutaneous tissue. The former was soft over the voluminous buttock, but harder on the thigh ; on the leg it was extraordinarily dense, fissured, and covered with firm protuberances. Overhanging folds concealed the foot down to the toes.

On a section being made, the hypoderm was seen to be thickened in places, as much as two inches, and consisted of cavernous tissue, which after division contracted, but only showed a few of the larger venous trunks. The intermuscular connective tissue of the thigh, the buttocks, and the pelvis, as far up as the region of the kidneys, was converted into a multilocular cystic formation, while the muscles and bones remained normal. The arteries showed no change ; the iliac vein, on the contrary, where it opened into the vena cava, was much larger than the latter vessel, and beneath the buttocks it received a number of veins, of the calibre of the brachial veins of an adult. On the anterior side of the leg, there were, on the contrary, no varicose veins, and the femoral vein even appeared narrowed. On the back of the leg, a new, abnormal, valvular venous system had developed. The cavernous tissue itself, with a low power, looked almost like an emphysematous lung.

Very much rarer is a *universal congenital elephantiasis, of an angiomatous nature.* Mandelbaum had a case of numerous flat nævi, scattered over the whole skin. I had the opportunity of examining a similar case in a four-year-old child, in which, however, the vascular dilatations were mainly subcutaneous. The extremities, especially the forearms and hands, were swollen, and, according to the temperature, dark or light blue in colour. The venous character of the soft, subcutaneous nodules, was evidenced by the incompressibility, and the absence of pulsation ; while their relation to the ordinary flat nævi was shown by the existence of a few smaller angiomatous moles on the hands, which passed into the deeper ones. Treatment had no influence on the affection, which was slowly advancing when the child suddenly died from intercurrent disease.

Where the influence of gravity acts very severely on ordinary flat nævi, a hypertrophy may take place in extra-uterine life, simulating elephantiasis. Thus we find described, tumours of the eyelid and the upper lip, which cover the whole or half of the face, and develope from simple, smooth, angiomatous moles of the lip or the lid. In such cases we have only an elephantiasoid degeneration of ordinary nævi, not a combination with a growing arterial angioma.

(f). *Elephantiasis congenita lymphangiectatica.*

This may be either universal or circumscribed. In the former category are placed non-viable monstrosities, which usually show other anomalies (Acephaly). Neelsen has very thoroughly examined a six months' fœtus of this kind.

> It was twenty-seven centimetres long, and showed a well-marked vesicular distension of all the parts of the body. The neckless head was larger than the spherically distended trunk, and covered, on forehead and occiput, with projecting swellings ; eyes, nose, and mouth almost disappeared between the distended cheeks. The short extremities were represented each by three round segments, the size of plums. Only on the palms and soles, and elsewhere where the skin is firmly adherent to the fascia, the œdematous character of the skin was absent, and there developed deep furrows, which separated the vesicular swellings.

Microscopical investigation showed that at the highest point of the swellings, the margin between muscular layer and hypoderm was blurred, and that the latter was distinctly margined from the cutis ; in less affected areas of the skin, remains of all three might be distinguished. These were all closely permeated by widely dilated lymph vessels, which, especially at the level of the deep cutaneous net, showed marked varicosities. In many parts the process had gone on to the formation of a cavernous lymphangioma, and these irregularly cystic spaces, which were in part to be made out macroscopically, gave rise to the spongy structure of the swelling. They were partly empty, partly lined with fibrin and cast endothelium. The blood vessels, particularly the capillaries of the surface, were wide, and contained numerous white blood corpuscles, which were only sparingly present in the tissue, and only in increased numbers in the neighbourhood of the vessels. The collagenous tissue showed no marked changes, and the fat lobules and the musculature were only separated by the enlarged lymphatic spaces. The epidermis was macerated, and in process of being thrown off, the commencements of the coil glands being drawn with it, while the lanugo hairs were still seated in the follicles.

At the highest part of the swellings, on the contrary, the connective tissue was very œdematous, and rarefied. The connective tissue cells near the spaces were ordinary spindle cells, and did not resemble the growing spider cells of myxomatous tissue. Here the fat had completely disappeared, the muscles had undergone granular degeneration, and the wide connective-tissue meshes contained, in some parts, coagulated blood. There was never any suggestion of progressive change in the connective tissue ; the condition was simply to be regarded as a passive combination of ectasis of the lymph vessels, due to the stag-

nation of lymph, with œdema and rarefaction of the tissue. The cause of this marked stagnation was not discovered; the combination of nephritic œdema in the mother, with special permeability of the fœtal vessels, and a scrophulous diathesis, to which Neelsen ascribes it, is too far-fetched an explanation. Any feasible hypothesis must take into account the cause of the stagnation. For neither a nephritic nor a tubercular hydræmia, though they may cause specific œdema of the skin, can produce such a marked lymphangiectasis.

Nor do we know the congenital causes of stagnation in those nearly allied, but circumscribed forms of elephantiasis lymphangiectodes congenita, which are described by Wernher as Hygroma cysticum. These are seen mainly at the neck and throat, more rarely in the sacral and perineal region of fœtuses, infants and children, and present soft, elastic, fluctuating, pretty large tumours, which do not diminish on pressure, but collapse after puncture. They consist of cystic dilatations of the lymph vessels and spaces, of very different size, some of which are closed, while others communicate with one another, but not with the lymph vessels; they are lined with endothelium. The cyst contents are usually serous, but may be sanguineous, or often a chocolate-coloured fluid; and in some cases the cysts are combined with angiomata. They occupy the region of the subcutaneous fatty tissue, which remains otherwise unaltered. The cutaneous tissue of the surrounding parts is usually thickened and firm, but does not show any capsule formed around the tumour.

From the cystic hygromata we must distinguish the branchial-duct cysts (branchiogenic cystic hygromata), which are clothed with cylindrical and ciliated epithelium.

More nearly allied to the cystic hygroma, is the more circumscribed form of the congenital, subcutaneous, cavernous lymphangioma. This usually forms discrete, soft tumours of the neck and axillary regions, more rarely diffuse swellings, which are especially seen on the cheeks and the trunk. In some cases they are in connection with deeper-lying sub-fascial and intra-thoracic lymphangiomata, and sometimes they are combined with a superficial papillary lymphangioma. In all cases the sub-cutis is converted into a coarsely porous, spongy tissue, which encloses more or less unchanged fat. Sometimes this directly margins the dilated lymph spaces, sometimes it is separated from them by a soft cellular tissue, which resembles that of a compressed panniculus deprived of its fat. The larger spaces are lined by true endothelium, and contain, in addition to serum and a few leucocytes, now and again fibrinous coagula, sometimes blood. The blood spaces are usually somewhat rounder than those containing lymph, and more approach the character of capillaries. The smaller spaces communicate with the

larger ones, and are surrounded by a highly cellular connective tissue; they usually have no endothelium, and contain abundant leucocytes, with which they are often absolutely filled. Where enclosed, leucocyte-containing spaces appear in sections, these are lateral sections of smaller spaces, whose opening of communication lies in another plane. When a papillary lymphangioma is combined with a subcutaneous, the cutis along the entire course of the blood capillaries is filled with leucocytes, and some dilated lymph spaces show the connection with the superficial new growth. But there is no true growth of the lymph spaces, analogous to that in angioma of the cutis. There is however sometimes combined with the lymphangioma, a new formation of fatty tissue, so that the greater part of the tumour is lipomatous; a combination of two stagnatory tumours, which is not uncommon. The hyperæmia seen in many of the cavities, is also a symptom dependent on the stagnation; Wegner and Nasse have recognised a subsequent filling of the lymph spaces from ruptured capillaries. The latter observer found in one case, the centre consisting of the larger cavities, still filled with blood, and the marginal zone with lymph, or coagulated lymph.

More frequent than in the non-congenital lymphangiomata, is the cystic form, which usually consists of a few, or only of one large cyst, into which the new formation has developed. These also are usually seated on the neck or in the axillæ.

The case of Langhans, which has become so important in the theory of lymphangiomata, may serve as an example of a third form of circumscribed, congenital lymphangioma. Here mainly the larger subcutaneous branches were affected, and the tumour extended only little into the subcutaneous fatty tissue, compressing and converting it into a spongy tissue. This form corresponds to the third group of the non-congenital forms of lymphangioma, including the case of Thilesen.

> In his patient (a boy), the tuberous thickening of the leg was noted at birth. The brownish, hairy skin was not œdematous, but the underlying fatty tissue was replaced by a spongy, lymphangiectatic tissue, which could be followed through the muscles, along the larger vessels, up to the upper third of the thigh. The swollen and reddened lymph glands could be injected more easily than in normal conditions, and the lymph trunks were everywhere permeable.

The new formation of lymph vessels in the panniculus, which usually contains no lymph vessels, Langhans ascribes to a growth of tissue, quite independent of stagnatory conditions—in contrast to Wegner's stagnatory theory of Macroglossia lymphangiectatica. This view is confirmed by the new formation of fibrillary connective tissue around the lymphangioma. The new formation of the lymph vessels is

thus explained, but not their dilatation, which, in subcutaneous vessels, reached $1\frac{1}{2}$ millimetres, and in the cysts which are occasionally seen, up to 5 millimetres. In my view, the whole new formation is explained by the co-operation of a congenital stagnatory cause, with a consequent vascular proliferation; and the extension of the lymph-angiectasis along the vessels of the thigh indicates the action of a central, congenital, stagnatory cause, in the left crural or iliac vein, which possibly was no longer to be recognised.

B.—Regressive Disturbances of Nutrition.

(a). *Congenital defect of the skin.*

H. v. Hebra has described a case of a healthy child, in which there were defects in the formation of the cutis on the scalp, consisting of various wide gaps, with narrow tracts between them.

The malformation commenced on both sides at the inner angle of the eye, extended directly backwards to the occiput, and was bridged here and there by healthy, hairy skin. It consisted of a reddish, soft tissue, in whose delicate epidermis, abundant quantities of fluid could be detected.

As the description and the very instructive drawing show, there were absent inside the tissue filling these spaces, all the epidermic structures, hairs and glands, as well as the panniculus, which was very thick in the surrounding scalp. The papillæ, too, were not developed; the epidermis was thin, but contained its three ordinary layers. The tissue of the spaces consisted of very œdematous connective tissue, beset by widely gaping lymph spaces, and penetrated horizontally by wide blood vessels, which gave off no branches to the papillary body.

v. Hebra assumes that there had occurred an arrest of development in the skin, and compares the condition of the epidermis with that in a two months', that of the cutis, with that in a six months' fœtus. It rather seems to me that in these spaces we have to do, not with a normal cutis simply arrested in development, but rather with a somewhat stretched scar tissue, which has arisen from granulation tissue filling the fissure. Thus the want of epidermic structures would not be remarkable; and it would be unnecessary to place the commencement of the process in the second month of embryonic life, as Hebra does.

It appears to me rather to be a healed embryonic "cutaneous defect," in the proper sense of the word.

(b). *Albinismus partialis.*

This is notoriously most frequent in the coloured races, but is not altogether absent in the white. A distribution in areas supplied by

certain nerves, as in the pigmented moles, is reported (Lesser). Hutchinson relates a case of linear Albinism in a negro, which exactly corresponded to the distribution of Nævus linearis.

Lesser had the opportunity of examining an area of partial Albinism, from the abdomen of a girl who died of phthisis, and found the skin absolutely normal, except for the absence of pigment. At the borders of the white spot, there was a very gradual transition into the normal pigmented skin, giving an exact antithesis to the accumulation of pigment seen in Vitiligo.

(c). *Poliosis circumscripta.*

The white lock among dark hair is a familiar occurrence, by no means rare in certain families, and is often seen in about the same situation hereditarily. So far as I know, there has been no histological investigation. It might give very important information on the question of pigmentation, for here there would be no other pathological process to confuse the matter. Poliosis must not be confounded with Hypotrichosis localis.

(d). *Atrichia localis, Hypotrichosis localis.*

Two cases of congenital, circumscribed baldness are described by Michelsen. In one of his cases, there was a small bald area over the right ear, which gradually increased with the growth of the child. I have also observed in a boy, from his first to his sixteenth year, in the same place, a bald spot of the size of a shilling, which slowly enlarged. It was gradually covered with fine downy hair, which in recent years has grown into long, white, completely unpigmented hair. This white spot is concealed under the thick dark hair surrounding it, and even yet seems thinner than the rest of the scalp.

In this case we have only a delayed and stunted hair growth, a hypotrichosis (Bonnet). The cause I would assume to be an atrophy of the affected region, caused by pressure between the fœtal and maternal bony surfaces.

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(e). *Atrichia, Hypotrichosis congenita universalis.*

Bonnet, in the course of a recent article on a congenitally hairless goat, also considers the cases of deficiency or complete absence of hair,

as it occurs in the human subject. This author suggests a practical division of these rare cases. They occur—(1) along with complete absence of teeth, or with irregularity in the formation of teeth or nails; or (2) as an isolated absence of hair, without malformation of teeth and nails; or (3) as a delay, and only later production of the hair (Hypotrichosis).

The first form is typically hereditary (Ecker's hairless family, Waldeyer), and indicates complete and congenital developmental incapacity on the part of the epiblast, as is evidenced by the simultaneous arrest of growth of all other embryonic epithelial structures. Jones and Atkins found in such a case, the cutis of the scalp replaced by an areolar fatty tissue, with suggestions of papillæ. There were the commencements of follicles, but they were pathologically altered. The epidermis was atrophic, and there was also malformation of nails and teeth.

In the second form, there is simply a malformation of hair. Schede published such a case, in which the head of the child was "as smooth as a billiard ball." The coil glands were normal, as were the very large sebaceous glands, which opened on the surface with wide mouths, and had a simple or composite formation. Hairs and hair follicles proper were completely absent. Instead of them, Schede found, deep down in the skin, close to the fundus of the sebaceous glands, peculiar epithelial tubes, without central cavities, without hairs, and without any connection with the surface epithelium, which showed outside, a row of cylinder cells, then a row of polygonal epithelia, and sometimes in the centre, onion-scale-like collections of smooth horny cells. Schede is inclined to regard these deep lying epithelial structures which produce horny cysts, as aberrant hair germs. Bonnet draws the conclusion in this case, from the presence of sebaceous glands, that at least there must be a separation of the hair germs into a prickle layer of the hair follicle, and a primitive hair cone, since the evolution of these always precedes the commencement of the sebaceous glands. Possibly, what occurs is a very early snaring-off of the primitive hair follicles, under the primitive sebaceous glands, resulting in an independent development of the upper segment into open sebaceous glands, and of the under into horny cysts.

In one case which I observed, in which, unfortunately, the excision of a piece of skin was impossible, I also found the follicular orifices on the very thick horny layer of the completely bald head.

To this form of fully developed Atrichia, we may compare, as a variety, Hypotrichosis (Bonnet), the delayed appearance of hair—that is, the transient, congenital absence of hair. Here the hair follicles are well developed, as are the hairs in them. But their appearance all over

the body, and especially on the head, is arrested by some restraint, or at least very much delayed. The cases resemble, microscopically and macroscopically, Hyperkeratosis suprafollicularis as described under the parakeratoses. At all events, Bonnet recognised similar conditions in his analogous case of Hypotrichosis in the goat: a superficial hyperkeratosis, especially of the upper part of the lumina of the hair follicles, spiral windings and coilings of the hair, consecutive bendings and dilatations of the follicles, and the formation of superficial hair cysts.

These cases are thus closely related to the previously described Hyperkeratosis universalis congenita. The case of Alopecia, noted under spindle hairs (Luce), also comes into this category. Here, as in Bonnet's goat, the hair cysts were to be found as conical papules with black heads, and one could extract from them rolled up spindle hairs.

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Section VI.

SAPROPHYTES AND FOREIGN BODIES.

It is in the plan of this work (Orth's Pathology) shortly to describe the foreign bodies of the different organs. But the external position of the skin permits such an inexhaustible multiformity of foreign bodies to enter into it, only a few of which have any pathologico-anatomical or microscopical interest, that from them we have to make a selection, which may be by the two conditions, of innocuousness and microscopical recognition. When a splinter penetrates the epidermis, and produces a phlegmon by simultaneous affection by pyogenic organisms, the process is one of purulent inflammation. And when, in examining normal or otherwise affected skin, we find saprophytes in the nails or in the mouths of the follicles (balls of cocci or acari), these also need not be considered, for they induce no clinically recognisable symptoms.

There remain then only certain affections of interest, which perhaps here require a short description. They may, of course, be separated into living and dead foreign bodies: Saprophytes and foreign bodies proper.

Under Saprophytes we have to understand those organisms and micro-organisms which, without inducing any proper skin disease, *i.e.* pathological alterations of tissue, vegetate in the skin. Strictly speaking, there is not an absolute integrity of the cutaneous tissue in these cases either. Even the perfectly innocuous human Acari dilate the mouths of the follicles, and Pityriasis versicolor separates the horny layers in its growth. We must then define saprophytes as inducing none other than mechanical changes in the structure of these dead or dying tissues (horny substance, sebaceous cells) on which they live. It is of especial importance that they produce no dangerous toxin of any kind, such as, for example, the itch mite, the staphylococcus aureus, and the morococci of eczema, and thus induce no inflammation; and that they do not give origin to progressive or regressive disturbances of the tissue. Of course cases occur in which it is very difficult to determine whether a slight degree of hyperæmia of the underlying cutis is to be regarded as its reaction to a small amount of

weak toxin, *i.e.* whether saprophytism or a very, very weak infectious inflammation is present, *e.g.* in Erythrasma. But as a whole, we can pretty well separate the saprophytes from the true disturbances of the skin, and it is one of the many advantages which we owe to Koch's work, that we understand these differences better than before. Pityriasis versicolor and Erythrasma are usually treated along with Trichophytosis and Favus, but from our point of view we must strictly separate them. Along with them comes Tinea imbricata, and, among the saprophytes of the hair which induce macroscopically visible changes, Piedra and Lepothrix.

As innocent and clinically recognisable dead foreign bodies, Tattooing and Argyria mainly attract our interest. But only the latter has been thoroughly investigated. On the diffuse yellow colour of the skin in Icterus, and the relation of the uric acid concretion to the cutaneous tissue, we have no definite statements.

A.—Saprophytes.

Pityriasis versicolor.

The spots of Pityriasis versicolor are induced by the presence of the Microsporon in the middle horny layer. The fungus never goes beyond the basal horny layer. Under its influence the whole of the middle and superficial horny layers swell up somewhat, and are loosened from the basal one, so that these layers can be removed *in toto*, along with the fungus, by a plaster. The clinical expression of this loosening of the horny layer is the slight scaling on scratching.

In this naturally pure culture, examined without any swelling agents, we see the almost continuous dense layer of fine hyphæ, interrupted pretty regularly by rounded deposits of spores, ten to fifty and more. The older and less disturbed the affection is, the larger and more numerous are the collections of spores. Now and again we see spores seated on the under part of the hyphæ, or proceeding from the hyphæ in rows; but the hyphal growth is always quite independent of sporulation. The hyphæ show fine, long, septate threads, which rapidly break down into their constituents, and rarely show branching. The free hyphal cells show a great tendency to bend, and often have the form of a V, which is no doubt due to a slight flattening in their diameter.

The isolated collections of spores without hyphæ are characteristic of Microsporon, as are the bent pieces of Hyphæ.

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Erythrasma.

Erythrasma is always found on the cruro-scrotal, or axillary contact surfaces, but it may extend beyond them. The surface is smooth or finely scaly, but the horny layer is not loosened as a whole, as in Pityriasis versicolor. The colour is coppery red to brown, but even in that case has more of a reddish tinge than in Pityriasis versicolor. It is distinguished from Trichophyton superficiale by the absence of any marginal elevation and vesicles, the duller monotoned colour, and the great chronicity.

The horny layer removed with plaster, shows the stained fungus as a dense felt of very fine, twisted and winding, rarely distinctly septate and non-branched hyphæ, which almost always show cylindrical swellings, and numerous fine, round or angular spores. This form, in distinction to Microsporon, shows no isolated collections of spores, but they are irregularly scattered, singly and in collections, between the hyphæ.

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Payne, Notes on some rare Skin Diseases. London, 1889.

Tinea imbricata.

An endemic fungus affection found in the Islands of the Pacific Ocean (Gilbert, Tokelau, Samoa), consisting of concentrically-extending rings of scales. It has usually been placed by English describers in parallel with Trichophytosis, although clinically it is more closely allied to Pityriasis versicolor, for, like it, it is a saprophyte of the horny layer of the surface, avoids the follicles of the skin, and commences with a brownish spot, which extends concentrically, and loosens the horny layer. But it is distinguished from Pityriasis versicolor by the macroscopically recognisable elevation of the horny layer, in the form of an elevated border. Since new processes continually spread from the centre—in contrast to ring-formed Trichophytosis superficialis—the whole surface affected by the Tinea imbricata—it may be the whole body—is ultimately occupied by movable, scaly rings, arranged like tiles. Towards the centre one can smooth them down, in the opposite direction raise them up; they adhere by their outer angles, and may be removed as continuous bands. Beneath the fungus

growth, in the coloured races, the pigment often transiently disappears, and frequently there remain leucodermic spots (Manson).

Königer and Manson discovered the fungus of this affection. The latter author, who named the affection and pointed out the distinction from English ringworm, gives the following characteristics. The conidia are oval, more rarely round or irregular; they are arranged in branching rows, and develope by the division of the mycelium or the conidia. In the youngest parts they are more rectangular, darker, and contain reddish brown granules. Larger spores are sometimes seated at the ends of the rows of conidia. These chains of conidia are more numerous than the mycelial threads. The mycelium is delicate, at most half as broad as the conidia, is much branched, and sometimes terminates in a conidial chain. Here also there are finer, unstained, and thicker ones, which contain reddish brown granules. The dried scales after some weeks no longer show conidia, but only broad, very much branched mycelium. From the trichophyton, this fungus is distinguished by the much longer, straight, non-wavy mycelial threads, and the enormous number of fungus elements in every individual scale. Here, also, Tinea imbricata rather resembles the other Saprophytes (Pityriasis versicolor, Erythrasma).

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Text-books: M'Call Anderson, Crocker.
MANSON, The Filaria sanguinis and certain new, parasitic, tropical Diseases. London, 1883.
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Piedra.

Piedra is a disease, endemic in Columbia (according to Behrend, also sporadic in Europe), which affects the hairs of the head, leading to small, stony hard concretions of fungus, externally adherent to the hair shaft.

According to Behrend, Juhel-Renoy and Lion, who cultivated the fungus, it is a thread fungus, which, in addition to very numerous spores, of irregular round or oval form, produces fine, segmented hyphæ. According to Juhel-Renoy and Lion, the latter also show true branching.

The spores are snared off like Oidia from the hyphæ; sometimes they multiply like yeast, by direct budding. According to photographs of the pure cultures by the latter author, the fungus most nearly resembles that of Erythrasma.

The fungus produces on the scalp no appearances of disease. On the hairs it produces more or less excessive splitting of the cuticula which may go on to that of the shaft; but the fungus itself does not penetrate into the hair shaft.

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Lepothrix.

This fungus growth, which E. Wilson called Lepothrix, is found on the shafts of the axillary and scrotal hairs, which are macerated by sweat, in persons who are not cleanly or sweat very much. It induces no symptoms. The hairs have no lustre, are rough and brittle. One may see and feel, on drawing them through the fingers, hard irregularities and nodules, which cannot be removed.

The nodules consist of yellowish, round, very hard protuberances, sometimes double the size of the hair shaft, which are seated directly on the hair, underneath one or two cuticular cells, just like buds. Cross sections of the hair shaft and nodules, show that the mass is not only seated on the shaft, but to a slight extent is rooted in it. It consists mainly of a homogeneous mass, very easily stained and very difficult to decolourise, which is surrounded outwards by a still firmer, double-contoured membrane. Inside the mass, some segments are coloured still more than the rest, and on decolourisation are seen to consist of oval, small, rod-shaped, bacterial elements. It appears to be a fission fungus, embedded in a very much hardened glœa. The resemblance to the American Piedra is evident.

The hair shaft undergoes a splitting only in its cuticle and outer rind, rarely a complete splitting. Its form is preserved by the very hard mass which sometimes completely surrounds it, but it is very brittle and easily torn. The growth of the affected hairs in no way suffers.

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B.—Foreign Bodies.

Argyria.

The deposit of dark silver combinations in the skin takes place either universally and indirectly from the blood, general Argyria, or directly from without, local Argyria or trade Argyria ; the latter has only been found in those workers with silver who have to work with powdered silver. This includes the local Argyria of the mucous membrane (Conjunctiva, Urethra), caused by excessive external use of caustics. General Argyria is usually most marked on the face and on the hands, but it spares no part of the body, not even the nail-bed. Trade Argyria has only recently become familiar, through the works of Blaschko and Lewin.

The deposit of silver, the silver combination, in the skin, follows a regular law. It is always limited exactly to the margin of the connective tissue, and especially affects the elastic fibres and the firm bounding membranes, avoiding altogether the protoplasmic parts of the connective tissue, and the epithelium with its appendages. We have from Riemer, Frommann and Neumann, three descriptions of general Argyria, corresponding in the main, which were recently confirmed, under Kobert's directions, by Krysinski. Frommann found that the macroscopical appearances were produced by a deep brown or violet streak, which ran along the surface of the cutis, exactly following the surface epithelium, but never going into it, except a little at the margin of the follicles. The same is true of the deposit of silver as of the melanotic pigment, that it opposes, so far as it can, the light; but in contrast to pigment, it evidently cannot penetrate into the epithelium nor into the lymph spaces. Since the silver probably reaches the skin from the blood, not as granules but as a soluble silver combination, we must assume that this silver solution cannot get into the neighbourhood of the epithelium. For were it to do so, there must appear in the transparent surface epithelium, a deposit of reduced silver. But the absence of silver in the epithelium can also not be due to the fact that the silver here is transformed into invisible combinations, for once deposited, it undergoes no further change. The absence of silver in the surface epithelium is consequently as obscure as the absence of pigment in many diseases, *e.g.*, Vitiligo, and we only know one thing definitely, that the ordinary separation of silver in the skin does not, as Loew states, follow the living protoplasm, for the protoplasm rejects the dissolved silver combinations.

Frommann found silver granules both in the membrana propria of the coil glands, and, in diminishing degree, in the ducts. Riemer confirmed this observation, and further, found all the layers of the follicle, especially the vitreous layer, then the membrana propria of the sebaceous glands, silvered. In the cutaneous muscles, he also found silver granules, and this was confirmed by Neumann; but these are also in connection with the connective tissue, perhaps the elastic fibres, not with the muscle substance itself. Riemer further found the silver precipitate in the whole cutis, in gradually diminishing degree; the papillæ contained masses of scattered granules; the arteries and capillaries were surrounded, but not the veins.

Neumann, who examined a much higher degree of Argyria, somewhat amplified these observations. He found the silver streak at the subepithelial margin, fifteen to sixteen millimetres broad, and from here the silver separation continued, though in much slighter degree, down to the fatty tissue, whose cells were surrounded by silver granules.

The coil glands were clothed by a completely blackened membrane, as were the sebaceous glands and hair follicles, which also contained silver. But the most important observation of Neumann was in connection with the elastic fibres, most of which showed complete sheathing by the silver. Finally, he also found silver in the walls of the veins, and in the neurilemma. Even in this marked silvering of the skin, the epithelia of the surface, the follicles and the coils, were completely free. The authors do not state anything definite of the amount of silver in the connective tissue cells. But their silence shows that these cells do not take up and reduce silver ;. had they done so, it would certainly have been mentioned.

Kobert found that all the black granules of the Argyritic organs, including the skin, consisted not of metallic silver, but of a loose silver (?) combination. If they have been caused to disappear (Neumann) in concentrated nitric acid or cyanide of potassium, the cutis at their seat still gives the albumen reaction, and blackens with sulphurated hydrogen. Kobert also recognised that nitric acid, although it caused blackening to disappear, did not remove the silver from the granules, but that this remained. From the circulating soluble silver combination, there is then formed, especially under the influence of light, or even without it, a very firm combination of certain albuminoid intercellular substances with silver, mainly collagen-silver and elastin-silver, while all the protoplasmic constituents, muscles, nerves and fat, reject the silver solution.

These results completely harmonise with the statements of Blaschko and Lewin on trade Argyria. Some of the silver fragments lie shining in the cutis, others are converted into black clumps and granules, whose nature cannot be completely determined (perhaps sulphide of silver, Blaschko). They are surrounded by violet collagenous bundles, diffusely argyritic and difficult to stain, and from these, bundles and nets of elastic fibres, impregnated with silver, radiate through the whole skin. Their elastic nature Blaschko recognised by their resistance to a 10% solution of caustic potash, in which the rest of the skin dissolved. Then there were also found scattered black granules, especially dense at the border towards the surface epithelium. This was as free from silver as the coil and follicular epithelia, and the connective tissue cells. This quantitatively different, qualitatively similar form of silvering of individual parts of the skin, whether in one case pure silver gets directly into the skin, or in the other, a soluble silver salt is absorbed from the intestine, shows that the black granules of Argyria are in no case transported, as such, to the place, but are taken up by certain constituents of the skin, according to their chemical characters, and that a chemical combination is formed.

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